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ON THE FACTORS CONCERNED IN THE ETIOLOGY OF RICKETS. +

by

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+Thesis for the degree of
Doctor of Public Health,
Submitted February 11,1921,
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BALTIMORE, MD February 11,1921

Dr. E.V.McCollum,
School of Hygiene and Public Health,
Johns Hopkins University.

My dear doctor:

In writing this paper, the undersigned had in mind the following: One must first know what the disease is, before attempting to determine its cause.Please allow meto invite your attention to the outline which is intended to illustrate this point.

The writer is aware of the fact that more stress has been laid on the clinical and pathological aspects of the disease than what otherwise might have been expected; but, in giving the right and honest treatment to the subject matter, and in order to understand more fully what the disease in question is, such could not be possibly avoided. And as the hope in the determination of the specific etiology of the disease seems to be in the way of animal experimentation, it is deemed necessary to give some discussion as to the behavior of the morbid process in the animal as well as in man.

With the above facts in consideration, please allow me to submit this small piece of work to you. Kindly allow me also to take the opportunity to express to you personally my hearty appreciation for your valuable suggestions and help in the present study.

Yours respectfully,

REGINO G. PADUA.

RGP/P

ON THE FACTORS CONCERNED IN THE ETIOLOGY OF RICKETS.

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ON THE FACTORS CONCERNED IN THE ETIOLOGY OF RICKETS

By Regino G. Padua, M. D., Dr. T.M.

I. Introduction.

In dealing with this difficult and obscure problem viz: "The Factors Concerned in the Etiology of Rickets," it is not the intention of the writer to add a very important item more than to present an analytical survey of what has been written on the subject during the last three centuries. He is, certainly, aware that future evidences may overshadow his personal views, but he also hopes that, similarly, experimental proofs may be forthcoming to support his contentions. The unbiassed would admit that, up to the present, no definite statement has, as yet, been made with regard to the exact nature of the cause of the disease inspite of the numerous scientific investigations that had been previously attempted. Of course, the valuable experimental works have undoubtedly cleared some of our doubts and advanced our knowledge; but if the results are not to be carefully correlated with the facts connected with the disease, the triumph of final solution can hardly be declared

safe until our mind is completely reconciled by the elimination of the gaps connected with the pathogenesis of the disorder. It is hoped, therefore, that the present paper may succeed in showing in a way some of what needs to be cleared out in the process of experimental investigation. But before undertaking this difficult task, it seems convenient to first summarize what th salient points are which may be collectively taken to constitute Rickets, in man and in lower animals.

II. WHAT IS RICKETS ?

A. In Man.

I. Definition .

The older writers had the tendency to regard Rickets as chiefly a disease of the bones--their studies of its etiology and pathology had been directed entirely in this particular line. But modern investigations have shown that although the main lesions are found in the bones still the distinctive features of the disease are not entirely confined in them. In other words, the term rickets can hardly be applied to the deformities and alterations of the bones without taking into consideration the change in other tissues that are also found in association with the disease. Again,the older investigators had pointed out that rickets resulted from various cuases, and not until recently, the food deficiency theory has been given sufficient attention. By these uncertainties which will be dealt with later, an exact definition of the morbid process can not, therefore, be claimed. But, ih the light of our present knowledge, we may briefly regard rickets as a constitutional disease, of usually early childhood, manifested clinically by the result of defective nutrition of practically all the structures of the body but chiefly of the bones leading to abnormal development of the growing elements, and,pathologically, by the faulty ossification and deformities of the active

portions of the osseous (skeleton) system, accompanied with other anatomical changes of the soft tissues of the body. In other words, there are to be found not only delayed dentition or fragile teeth, symptoms referable to wasted and weak muscles, relaxed ligaments, catarrhal condition of the mucous membranes, abnormal irritability, anaemia, and, in some cases, abnormal structural alterations in the viscera, but also an arrested or delayed calcification of the growing portion of the skeleton leading to various deformities particularly of the chest and head, and epiphysis of long bones, accompanied by distortions, and sometimes fractures of the shafts. These morbid processes may probably be the result mainly of dietetic error, besides other predisposing factors, where the organism is not receiving its adequate food constituents essential for physiological growth and metabolism.

2. History of the Disease.

It is interesting to note that Barlow and his co-worker[1] regarded the disease as "probably coeval with civilization", that is, the former seemed to have increased in frequency hand in hand with the progress of the latter.

The classical description of Glisson in collaboration with his contemporaries Bate and Regemorter, in his famous treatise, " Tract. De Rachitide seu morbo puerorum qui 'The Rickets '

di~~s~~citur" published in London in 1650, has established the morbid process as a distinct clinical entity and has brought it to the attention of the medical profession.[2] That the disease might have been existing but unrecognized long before Glisson's time, may be shown by certain references in the earlier writings. Findlay[3] says that Homer had described in the Iliad, written 900 B.C., the court jester as "bandy-legged, lame of one foot, etc" with other signs which had been interpreted as typical picture of rickets. He[3] also remarks that Saranus Ephesius who lived between 98 and 138 A.D. and practised as a physician in Rome, has written a book entitled, "Diseases of Women" where, in some chapters (as "How should the child be trained in standing and walking?" and "Why the majority of Roman children are distorted,")

references may be made which he[3] emphatically regards as being rachitic; contrary to the description of early Greek writers as Zesas on the history of the malady where the latter cited passages in Hippocrates' work "De Articulis," which might be taken to mean a tubercular disease of the spine rather than rickets. That the disease has been existing before the middle of the 17th century, is similarly shown by Moore,[4] ~~and~~ in his thesis where he calls attention to the paintings and descriptions of antiquity, and references in Theodosius' writings in 1540, viz: "The complaint is a weakness and inability to move so that this child of 17

months old can, in no manner, move itself, nor stand, and when it is carried in the nurse's arms, it can scarcely hold its head upright. Another symptom, the most cruel of all, is that three of the vertebrae of the true ribs bend outwardly to form a kind of humpback, and the ribs appear to be arched in the manner of a bow."

The traditional name, Morbus Anglius (which may be taken as a synonym of rickets) or English Disease probably because of its prevalence in west of England at the time of its recognition as a definite clinical entity, is believed by Fagge[5] to have originated from the title of the treatise published by Whistler at Leyden in 1684, "De Morbo Puerili Anglorum". The erroneous idea, however, that the latter author (Whistler) was the discoverer of the disease because of his inaugural dissertation on rickets in 1645 entitled, "Poedosplanchnosteoceae" was strongly denied by Moore[6] in the discussion on the Pathology of Rickets held on November 16, December 7 and 16, 188o, where he says:

> "Glisson is known to have been at work on rickets in 1645, and he published his work on it in 1650, a book which marks the dawn of medicine after the darkness of the middle ages."

Glisson was, therefore, the first to give an accurate description from both the clinical and pathological standpoint, identifying the disease under the name of "rachitis". The first chapter of his precious book dealt with the name and origin of

of the malady[4]. At his time, the disease was commonly known to the laity as "the rickets"which is believed to have been derived from the old English word "wrikken" meaning"to wrest" or"to twist". Glisson proposed the word Rachitis for Rickets, partly due to the similarity of the sound and partly as a derivative from the Greek word ῥάχις meaning "spine", on the ground that the dorsal spine is one of the first parts attacked.[7] In the 1st chapter of his book, Glisson regarded the disease as having originated in the counties of Dorset and Somerset, whence it spread to Europe, although Cheadle[7] believes that the disease might have existed on the continent "from the early times as an accompaniment of civilization." By a further study of Glissan's treatises, one would be so impressed of its accuracy and thoroughness as to justify Findlay's[3] assertion that the book is a "monument to English Medicine for all time."[4] Moore who made such an analytical survey of Glisson's work in his thesis on "The Cause and Treatment of Rickets", points out that the second chapter deals with the post mortem appearances, the chief points of which are : "large head, wasted muscles, loose skin, enlargements of the ends of the bones, deficient rigor mortis,pigeon breast,ribs with beads, and distended abdomen". The next twelve chapters, particularly the following five treat of the cause, affinities and other topics essential in the investigation ofthe disease.

Chapters XX, XXI, XXII, and XXIII deal with the varieties,

symptoms, diagnosis, and prognosis of the malady. The symptoms are accurate and too long to enumerate but the salient points are:

> "The skin and flesh are less firm than natural, the joints weak, the body bent, the child learns to walk late and is averse to being shaken. There is pigeon breast, the abdomen is swollen; very often there is cough; the child will not lie on either side but only on its back; the pulse is feeble; a moderate ligature tied about the limbs causes less swelling than in a healthy child; many bones bend, most often the tibia, fibula and radius--less often the humerus and femur; the long bones sometimes do not grow; the bones of the forehead stick out. The teeth come slowly and soon rot; the head is big, the face full; there is swelling of the wrist and less often of the ankles."

Under prognosis, Glisson remarks that "the disease in its own nature is not fatal."[3]

The publication of Glisson's incontestable treatise in 1650 was followed by numerous scientific articles on the subject written by prominent investigators of the time, among whom Moore considers the following seven as "faithful guides for practical study", viz: the works of Sydenham, Boerhaave, Guerin, Beylard, Trousseau, Jenner and Gee. Among other Fellows of the Royal College of Physicians who have written on the disease were Scheafe, Wright, Padget, Goddard and French.

It is also of historical interest that Glisson considered the disease as caused by many factors[2], but lays stress on heredity[3]. Former investigators on rickets held different

views regarding its etiology and pathogenesis; but they may be summarily grouped into two main classes: (1). Those who maintain the defects of hygienic environment such as will be dealt with later including the "Domestication Theory" of von Hannsemann and "the respiratory poison theory" of Kassowitz (quoted by Hess and Unger[8]), and (2) those who uphold the theory of dietic errors including the fat deficiency and the alimentary intoxication theories. But since the time of Glisson, no definite advance can be noticed until recently when, in the careful study of this so-called deficiency theory, the experimental speculations on the "vitamines" were beginning to disclose little by little what we think to be the underlying secret regarding the mechanism of how the disorder may be brought about.

3. Diagnosis.

The recognition of the disease in man can only be safely and properly made by an accurate knowledge of its characteristic behavior in the individual. To the practitioner, as well as to the experimenter, a careful study of its clinical and pathological aspects would, in my opinion, be indispensable; and, in the present paper, it does not seem out of place to point out the important points connected with the Symptoms and Pathology of the Disease.

a. (1) Coastitutional Symptoms.

Barlow and Bury[1] have expressed what seems to be the right[illegible] view:

> "There is, in fact, scarcely any chronic disease which shows more quantitative variations than Rickets, going down to a vanishing point which needs the greatest care in order to establish its existence, and having in its mildest form a duration perhaps of only a few weeks."

It is a fact, as is admitted by clinical authorities, that the disease may exist unnoticed in an individual and, oftentimes, when it begins to be recognized, ~~by the practitioner~~, the morbid process is usually moderately advanced in its course. Such early signs, therefore, even in the absence of subjective symptoms, namely,: hyper-irritability and restlessness of the child, nocturnal sweats in the head and heck, tendency to catarrh,and slight beading of the ribs, should serve as warnings and be considered suspicious until other condition giving similar clinical picture is otherwise established.

The disease has an insidious onset and a chronic course. But usually it begins to manifest itself within the first two years of life. Mild cases may, however, be overlooked. ~~so that when one establishes a diagnosis of rickets, the disease has, for sometime , being doing its usual ravages~~. Gastro-intestinal disturbances may or may nor precede the appearance of the characteristic lesions. However, the rickety child exhibits,as a rule,

an extraordinary liability to pulmonary and intestinal catarrh.[1& 4]

When the disorder has fully established itself, the following constitutional symptoms may be observed. There is restlessness, ill temper and inability to sleep; oftentimes the child throws off the bed clothes even when the weather is cold, and cries even at a gentle touch or slight provocation. Osler,[9] contrary to the opinion of Findlay[3] , believes that there is usually a slight fever accompanying these nervous manifestations. The existence of general pallor and muscular flabbiness is not invariable. However, excessive perspiration about the head and neck, especially when the child is asleep, is a more or less constant finding. When the child has learned to sit up or walk, it exhibits a disinclination to do so; in fact, the general weakness may be such that it cannot even support its head erect.

a. (2) Physical Signs .

The Head.

By close examination of a rachitic head, one would be impressed of its square configuration, hence the term *caput quadratum* has been given. This deformity is due to the abnormal bulging of the parietal and frontal eminences which authors speak of as "cranial bosses", and an apparent flattening of the region of the calvarium. At the back part of the head (occipital region), there is usually an ~~slight~~ area where the hair may be scarce or

totally lost. This is due to constant pressure on and friction against the pillow as the child shifts from side to side during the state of restlessness.

The head is larger than normal but the face is relatively smaller than usual; so much so, that it has been mistaken for chronic hydrocephalus. The latter condition occurs quite independently of rickets, and is entirely a different morbid process. The enlargement of the head appeals to Barlow and Bury[1] to be mainly explained by the delayed ossification of the sutures, and by the massive thickening of the cranial bones. By palpation, there may be thickening of the growing margins of the cranial bones; i. e., at the edge of sutures, and the anterior fontennelle which normally closes at about the age of from 12 to 18 months[3] may remain widely patent and may persist to be more or less open until two or three years of life, or even as late as five years.[7]

While there are undue prominences of the frontal and parietal bones due to hyperplastic changes of the cellular elements,[1] there may be felt on the skull, thinned portions or atrophic afeas which give to the touch the impression of parchment-like paper as they yield to even a slight pressure. These tabetic patches are usually perceptible in the parietal and occipital regions. Elsässer[10], who first described the condition lengthily in his famous pamphlet, regards craniotabes as essentially of the nature of rickets. Quite a number of prominent writers have held the same view. Lee and Barlow[11], on the other

hand, who investigated the subject among 100 cases of rickets, have observed that 50% of the children with obvious craniotabes, and 40% of those in whom the condition was less prominent, were syphilitic. They also showed that craniotabes is not simply a condition of marasmus, and in their conclusion, they say:

> ".....that syphilis is by far the largest factor in the causation of craniotabes, ...At all events, our observation shows that the existence of marked craniotabes must be regarded as affording strong ground for suspecting the existence of syphilitic taint."

Again, Barlow[12] in a separate communication, presnted a ~~difficult~~ typical case of craniotabes on the left parietal bone without the slightest manifestation of or history referable to Rickets, but with some ground that it was syphilitic. However convincing were the views regarding the association of syphilis and craniotabes, Parker[13] and others maintain Elsässer's opinion and cite cases with well marked tabes but without any history or signs of syphilis whatever. Moreover, Findlay[3] states that he has seen "undoubted craniotabes in non-syphilitic infants" and that in Europe, the opinion of the rachitic origin of craniotabes was so strong that a change of the condition has been frequently taken as index to the efficacy of the anti-rachitic treatment. There can be no doubt therefore, that, although craniotabetic patches may be found in syphilis, it is equally possible that similar condition may be met with in rickets. Moreover, there are no evi-

dences to disregard the possibility of rickets and syphilis coexisting in the same individual.

The apparent enlargement of the head over the normal size has led some to believe that rachitic children are endowed with mental superiority. Thus Lucas[14] regards the rickety skull, as a gift because of uts capacity for greater mental development. Parker[13] and Moore[4], on the other hand, frankly express that they failed to find the mental superiority of rickety children over others and cannot admit it as an invariable condition associated with the disease. On the contrary, it seems to be the common opinion of a number of writers that there is a lack of mental alertness in rickets. Sir William Jenner[15] in his third lecture on Rickets, says:

> "Children, the subject of extreme rickets,
> are almost always deficient in intellectual
> capacity and power."

Likewise, Palm[16] holds that mental apathy is a striking feature of the rachitic child. Intellectual development, therefore, may show wide variations and it is difficult to ascertain whether or not the possible deviation from the normal may probably be brought about by some such anatomical alterations of the brain substance, as Jenner[17] seemed to have pointed out, or to functional derangement subsequent to the lack of stimulating influences from without or to the state of nutrition of the individual.

In rickets, dentition is usually delayed and if the teeth have already come out, they are often brittle and subject to decay. May Mellanby[18] made an exhaustive investigation on the relation of defective teeth to rickets, whereby the two conditions may be placed on an experimental basis. She showed that similar factor or remedy which would prevent one condition would almost always improve the other. Likewise, she pointed out that the incisors, the canines, and the first molars which are in the state of active ossification from the ninth month till the end of the second year of life,are the ones most likely to undergo carious changes at this age. The majority of rachitic individuals or of those who have had rickets, show defective teeth. The relationship of the two disorders seems to be so important that Edward Mellanby[19] remarked:

> "The rachitic child, in fact carries the stigma of the disease throughout life in the form of defective teeth."

The Chest.

One of the most striking features of the disease is the deformity of the chest wall. There is usually a flattening of the sides of the chest with a corresponding projection of the sternum,thus simulating the "pigeon breast";or the flattening may amount to a contracture so that there may be an ~~natural~~ actual de-

pression on both sides to receive the name "violin-shaped" chest. Stoelzner[20] describes the mechanism of the thoracic deformity in rickets as follows:

> "The deformity of the thorax in rickets is caused, on the one hand, by the abnormal weakness of the chest wall which yields in time to the diaphragmatic contractions at each inspiration and to the elastic pull by the collapsing lungs at each expiration, and,on the other, to the continual pressure exerted by the overlapping upper arms. The flattening of the posterior chest wall is the result of the continuous dorsal decubitus. The bulging of the costal margin is caused by the rachitic enlargement of the liver".

But whatever the mechanism be, the resulting deformity does not seem to be an invariable finding in every rachitic child. To the question raised by Fagge[5] : "Is it certain that pigeon breast is ever seen in a child whose bones are absokutely healthy?", Moore[6] offers an answer by citing a case of a severe whoopingcough without symptoms of rickets,which subsequently developed in three months' time, a distinct pigeon breast. Similarly, Jenner[17] states:

> "In reference to the pigeon breast, I would say that it often arises from other diseases than rickets.... The two varieties are very easily distinguished."

It may be safely stated, ~~therefore~~ however, that pigeon breast,despite

the posssibility of other thoracic conditions giving rise to similar deformities, is not an uncommon finding in rachitic cases.

The thoracic disfiguration is not infrequently accompanied or aided in its formation by the appearance of a row of knobs or nodules at the junctions of the ribs, especially the lower ones, with their correspinding cartilages. These"rachitic rosary" or "rosary beads" which are regarded the earliest of bone changes and may be one of the earliest clinical manifestations of the disease, are, in the opinion of Fagge[5], contrary of that of Cheadle[7] and Moore[4], enlargement of the costal ends of the cartilages rather than of the ribs themselves. The beading of the ribs is considered so important in the eyes of the clinical men that Barlow[12] speaks of the following:

> "The fifth and sixth ribs on the inner surface are test ribs for rickets, and if a child seven months old has any rickets at all, it will manifest itself in this position."

While it has been generally admitted by the pediatricians that rickety rosary is a pathognomonic sign of rickets, Hess and Unger[8] claim to have found among their infantile scurvy cases similar manifestations and emphatically state :

> "In other words, there is not only rachitic but also scorbutic beading."[8]

and then they say :

> "It was pointed out by Jackson and Moore and has been noted by various other investigators, that beading of the ribs occurs in the course of experimental scurvy of guinea pigs.........We have encountered similar beading, with slight hemorrhages in the costo —chondral ~~region~~ junctions, in the scurvy of dogs."

The beading of the ribs may also be found in deficiency diseases other than rickets and scurvy. Andrews[21] found among his eight cases of infantile beri-beri,three who exhibited distinct beading of ribs. But the existence of beading in other deficiency diseases, does not invalidate the formation or occurrence of ~~similar changes~~ it in rickets; so frequent and close is its association with the latter, that the rosary has been regarded of considerable diagnostic importance contributory to other manifestations referable to the disease. *Moreover, it seems rather questionable whether or not in the above cases rickets has not been coexisting. In some instances,* a row of ~~rachitic~~ rosary beads along the posterior axillary line *may also be observed.*

On the inner side of the row of rosary beads, one may perceive a distinct depression or groove obliquely placed on the chest wall.This may or may not be accompanied by a more or less exaggerated curvature of the cartilaginous portion of the ribs. Still another depression may be seen from the xyphoid process transversely on each side of the chest at about the level of the diaphragm to the posterior axillary line; this is known among the clinicians as the "Harrison's groove ", also of diagnostic significance,which,in the opinion of Findlay[3], is

brought about chiefly by atmospheric pressure.

The Abdomen.

Due to the laxity of the abdominal muscles and probably to some intra-abdoninal pressure, the abdomen may be seen bulging. The pressure from within may be partly due to the probable enlargement of certain visceral organs as the liver and spleen, or to the distension of the bowels due to the loss of tonus of the muscular wall, or both. Smith[22] adds another factor that contributes to the protrusion of the abdomen and that is the rachitic curvature of the spinal column. The liver and spleen may become palpable to a lower level and appear to be larger than normal. The pathological significance of these two organs will be dealt with later; but it suffices to say that the sign may not mean actual enlargement but simply a displacement of these organs subsequent to the contraction of the chest walls and of the diaphragm.

The pelvis may be seen disfigured as a result of the deformities of the sacrum and the ossa innominata. The mechanism of the deformity will be described later but for the present, it is noteworthy to consider the reduced pelvic outlet resulting therefrom as a guide in advising marriage among women who had been attacked previously with the disease.

Extremities:

The signs in the extremities consist of enlargement of the ends of the long bones and curvatures along the region of their shafts. Moore[4] opines that the bones are affected in chronological ordef, viz: Tibia, bones of the chest, the arm bones, and the femur. We have, therefore, an enlargement about the ankle and wrist joints from the enlargement of the ends of the tibia of one and of the radius and ulma of the other. Lucas[14] says that the enlargement of the wrist is more than that of the ankle in the crawling child.The enlargement is specifically located at the region occupied by the junction of the epyphysis and the shaft of these bones. Similar thickening or enlargements may be seen about the elbows, knees, carpo-metacarpal, and metacarpo-phalangeal joints.[1] And Lucas[14] found the "knock-knee tubercle" and claims it to be an important and new sign of the disease.

It is not uncommon to find in rickety individuals abnormal curvatures, not only of the ribs but also of the long bones of the limbs. This deformity results from the yielding of the weak bone to muscular effort or outside influences as walking or crawling. When the patient stands up there may be observed bowing of the lower limbs; genu valgum or genu varum results depending upon whether or not the patient has been walking or crawling. If the rickety child is carried in the arm, Barlow[1] thinks that the femoras become arched foreward with a marked convexity

foreward in the lower 3rd of the tibia. These abnormal curvatures and the delayed growth of the long bones characteristic of the disease contribute to the development of dwarfism of the rachitic skeleton. The state of development of the bones of the chest, limbs and face of the rickety child is not, however, in conformity with but rather in inverse ratio to the abnormal enlargement of its cranium so that the patient is misshapen and apparently out of proportion altogether.

It is not ~~however~~ altogether very infrequent to find a fat rickety child instead of an emaciated one. Thus Barlow and his co-worker believe that fat rickets is more common that thin rickets; and that only in severe or prolonged cases when emaciation supervenes. And they say:

> "Rickets is rarely initiated and rarely very active during a period when severe wasting of the tissues of the body from any cause occurs."

Jenner[17] likewise upholds the same view and says:

> "Many rickety children are exceedingly fat, and I do not regard emaciation as due merely to rickets, but to the changes of the internal organs, especially in the lymphatic glands. Similar changes in these glands lead to emaciation in older children."

The question of whether or not a rickety infant is fat or emaciated is of little clinical or diagnostic importance for, although the normal contour of the body may be maintained in

he first or mild stages, in the prolonged or severe type of the disease, cachexia may subsequently follow.

The weakness of the limbs due to flabbiness of the muscles and laxity of the ligaments, is characteristic of the disease. Howard[23] considers the changes in the muscles and ligaments as essential as those in the bones, and says:

> "The inability to walk is not because of the changes in the bone, which are palpably coincident, but because of the muscular weakness, which shows itself in other ways--e.g., the bowed spine of rickets depends upon the weakness of the spinal muscles, which are not strong enough to keep the spine erect........The knock knee and the flat foot are other instances of muscular weakness".

Probably as a result of the lack of tonus of the spinal mjscle, the unnatural posture of the child, and the deformity of each individual vertebrae, the spinal column may be seen curved abnormally, such as kyphosis generally in the dorsal region, and lordosis usually in the cervical and lumbar regions, but rarely scoliosis ~~and~~ which, if so exist, Smith[22] believes it ~~was~~ to be due to the nurse carrying the infant in one arm. Jacoby[24], on the other hand, thinks that scoliosis and strabismus are common in rachitic children and says:

> "Habitual scoliosis of the very young, up to the 10th year, is almost exclusively muscular, mostly dorsal or sometimes lumbar, with the convexity usually to the left."

The flabbiness of the muscles is not confined alone to the skeletal but also to the intestinal muscle tissue. There may be expected therefore a paresis of the gastro-intestinal peristalsis. Jacobi[24] who investigated the question of muscle of rachitic infants expressed the opinion that the resulting constipation favors the absorption of harmful or toxic products from the decomposed feces whereby "more symptoms of rachitis will soon develop". He differentiates rachitic and congenital constipations and believes that in rickets there is a distinct chemical alteration of the muscles. He further points out the importance of rachitic constipation in the early diagnosis of rachitis so much that after excluding all other possible causes for the condition and in the presence of other symptoms referable to rickets, the anti-rachitic treatment may be justified.

While Jacobi[24] considers constipation as a distinctive feature, Cheadle[7] and others speak of laxed bowels with loose and offensive stools. Likewise Fergusson[25] who made an extensive statistical study relative to the causation of rickets found that, among her Glasgow cases, 32.6% gave a history of diarrhoea. She believes, however, that the difference is too small to justify a sound conclusion and suggests "that further study should be given to the relationship of intestinal troubles to the onset of the disease." But whatever the associations be, there can be no doubt that in a well established rickety case, the gastro-intestinal

tract is easily prone to catarrh. There may be, then, either constipation or diarrhoea although Findlay[3] states that in the majority of his cases, digestion has been normal.

(3) Associated Conditions.

The proneness of the mucous membrane to a catarrhal inflammation is not only exhibited by the gastro-intestinal tract. Symptoms of bronchial catarrh in the form of bronchitis, broncho-pneumonia, collapse and compensatory emphysema and other lung affections are not uncommon. The tendency to pulmonary disorders may be the result of mechanical pressure of the deformed chest[3] or to the inefficiency of respiratory mechanism.[7]

It is not uncommon to find associated with the disease nervous manifestations. Hyper-excitability of the patient, restlessness and inability to sleep show an implication of its general nervous mechanism. There may be laryngismus stridulus, and various other spasms, reflex or otherwise, such as tetany or general convulsion.

The above are the symptoms and signs which must be borne in mind in the diagnosis of the disease in man. They present a distinct clinical picture different from those of scurvy or osteomalacia which may be confounded with it. The so-called acute rickets alluded to by prominent investigators has been

found to be infantile scurvy. In this connection Holt[26] and his co-worker seem to have expressed the most desirable view when they say :

> "Although from time to time cases have been reported with this title, from a study of the histories, it is clear that the great majority, if not all of them, were cases of infantile scurvy. It is doubtful whether, strictly speaking, there is such a thing as acute rickets."

It is needless here to give the differential characteristics of scurvy and osteomalacia as these diseases may be found described in text books of Pediatrics or of Internal Medicine. Furthermore, a thorough knowledge of the above symptoms would enable one to separate rickets from any other allied morbid coddition.

a. (4) Blood Examination.

One thing, however, ~~that~~ needs to be cleared up before going into the subject of Pathology of Rickets, and that is, the blood picture associated with the disease. There is much discussion as to whether or not anaemia exists in rickets. Jacobi[27] in his work on the "Blood and Circulation in Rickets", says:

> "In rickets, anaemia, or rather hydraemia, is common."

[27] He points out that the red cells may go down within three weeks from 2.11 million to even as low as 750,000 per cubic millimetres, and in these cases 30% to 60% hemaglobin; while the leucocytic

count may increase to 25 or even 26 thousand. The increase, according to him[27] "is caused by polyneuclears and neutrophilic cells, and does not depend on complications, for instance, with intestinal disorders". Likewise Holt[26] maintains the view that there is anaemia in rickets and explains how it is partly brought about:

> "The normal red marrow may cease a quarter of half an inch from the epiphysis, its place being taken by a light grey or whitish layer that microscopically is seen to be fibrous tissue. The replacement of so much marrow is perhaps the reason for some of the anaemia that is prominent in severe rickets."

Cheadle[7] asserts that anaemia is, as a rule, proportionate to the other changes characteristic of the disease. Similarly, Goodhart[28] affirms that the blood changes are not invariable; and says:

> "In some there was simple deficiency of corpuscles, in others, deficiency of coloring matter."

But, according to him[28], the most remarkable change is the variety of sizes of the red blood corpuscles with certain quantity of free granules in the circulating plasma. On the other hand, Findlay,[29] as a result of his observations among rachitic and non-rachitic patients attending the outdoor department of the Glasgow Hospital for Sick Children, asserts emphatically that there is no anaemia connected with the disease. His exhaustive studies on the Blood

in Rickets led him to the following conclusions:

> "1. In active and uncomplicated rickets, anaemia is not the rule but is to be regarded as exceptional and when it occurs, due to adventitious causes.
> 2. On the contrary, in rachitic children the amount of hemaglobin and the number of red cells in the series examined are notably in excess of the normal average.
> 3. The red blood corpuscles, as a rule, vary more in size than in normal individuals of similar ages, but ~~lik~~ otherwise there is no abnormality.
> 4. Nucleated red cells, polychromatophilia, and myelocytes are of the rarest occurrence.
> 5. In rickety subjects there is little characteristic change as far as the leucocytes are concerned. They may be normal, slightly increased, or even diminished in number. The mononuclears more frequently than the polymorphs show an absolute increase in number per cubic millimeter."

These conclusions would have been more convincing if the blood picture of the rachitic patients had been watched and checked by subsequent blood examinations of the same individuals during convalescence or after the attack. As it is, the question is open: Did the blood findings return to the normal? So that, as a whole, in view of the foregoing conflicting ideas, a definite statement as to whether or not anaemia is an invaluable finding in rickets, can hardly be given safe until justified by the results of subsequent re-investigation of the subject.

b. Morbid Anatomy.

Having thus far established the clinical picture of the disease in man, the question arises: What are the corresponding anatomical changes? As may be deduced from the preceding descriptions, the symptoms of rickets are not only those referable to the derangements of the osseous system but also those of the soft tissues. Therefore, the patholigical changes are expected to be found in both tissues, although those of the bones may be the most important.

(1). Leaions of the Bones.

Perhaps, the most characteristic and more or less constant lesions so far determined in rickets are those of the bones. The flat bones of the skull as well as the long bones ofthe chest and of the extremities are equally affected.

(1) (a) Gross Anatomy.

By careful study of the osseous changes in rickets, one may note that the bones of the skull and of the extremities present comparable or identical lesions,[17] which may be summarized as those due to faulty ossification, delayed growth, and subsequent deformities. The thickening of the margins of the cranial bones, devoid of osseous material, and the existence of excessive amount of unossified tissue at the region between the epiphysis and the diaphysis of the long bones, show that the ossification

of the growing portions are at fault. This type of lesion seems to be worse, the more rapidly growing the individual is. The normal osseous expansion of the calvarium on one hand and the proper elongation of the long bones on the other are, consequently, prevented. This explains the wide sutures and the enlarged fontanelles, and the tendency to dwarfism in rickets. The deformities of the long bones will be dealt with later, but for the present, let us briefly point out what those of the skull are.

The cranial bones seem to exhibit two types of lesions, namely: those referable to proliferation, and those to atrophy. As has been remarked above, the head of the rachitic child is proportionately larger than that of the normal. Whether or not there is an intracranial pressure tending to dilate the sutures and enlarge the size of the head, is still a question to be solved. However, there can be no doubt that the apparent enlargement is due partly to the presence of the cranial bosses. These abnormal prominences in the frontal and parietal and sometimes in the occipital bones, have been regarded by Barlow and Bury[1] and Cheadle[7] as the result of a hyperplastic change (hyperostosis) developed chiefly from the outer table of the skull, and "consist of red, very vascular spongoid material, which can be indented with the finger or easily cut with the knife." The other type of lesion (the atrophic) is the formation of thinned spots scattered in the parietal and occipital bones. Elsässer[10]

first described the lesion, but it is a matter of dispute whether or not craniotabes is invariable in an uncomplicated rickety skull. But, whatever the view held, these tabetic patches may be most likely due to imperfect growth or delayed ossification of the cranial tissue rather than to the pressure of the brain or of the pillow.

The bones of the face also suffer the consequences of defective ossification. It has been remarked upon that the face appears to be relatively smaller in comparison to the enlargement of the head. As the bone changes in rickets are generalized in the whole skeletal system, it is not unlikely that the facial bones may exhibit marked deformities similar to those of the extremities. The teeth, as has been remarked, are not infrequently attacked. As has been shown by Mellanby,[18] many of the rickety cases exhibit carious teeth. In other words, the rickety tooth lacks the support of its integral well-being and is prone to rot. It is devoid of its enamel coating and becomes so brittle that it may break even with slight effort.

The abnormal curvatures of the vertebral column have been described under Symptoms. The gross changes in the individual vertebrae are similar to those of the other rickety bones and consist of faulty ossification and subsequent deformity. Moore[6] calls the attention to one anomaly in the vertebral body

which he found in a large number of cases and that is, the heaping of bone at the edges of the vertebral centra". In this connection, he[4] says:

> "The vertebrae project internally above and below each inter-vertebral substance. This I have not found noticed in any author, but have observed in every post mortem examination I made."

The pelvis also suffers certain deformity. There may be diminution of the antero-posterior diameter of the pelvic brim subsequent to pressure of the abdominal organs tending to widen the border on one hand and to the pressure of the spinal column sustaining the body weight thus pressing forward the promontory of the sacrum on the other. These factors, in conjunction with the upward pressure offered by the heads of the thigh bones in supporting the body erect, tend to diminish the pelvic outlet. The resulting deformity is of considerable importance from an obsetrical standpoint.

The most significant lesion is perhaps that of the long bones. This refers to the ribs as well as to those of the extremities. The enlargement of the costo-chondral junctions have been referred to under Symptoms. But inasmuch as it seems doubtful whether or not rickets alone produces the characteristic beading invariably, it is equally questionable whether or not the individual bead or nodule arises from the cartilage alone[5] or from the growing end of

the rib bone alone[7], or from both[4]. At any rate, the rachitic rosary seems to be larger in the costo-chondral junction of the lower ribs and more prominent on the inner than on the outer aspect of the bone. The beads seem to correspond with the enlargements of the area between the epiphysis and the diaphysis of the long bones of the extremities which will be desctibed shortly.

The long bones show exaggeration of their normal curvature This condition has been referred to as caused by the single or combined action of muscular contracture, atmospheric pressure(ribs), unnatural position of the patient, weight of the body or of the limbs themselves on the already weakened,deficiently ossified, flexible, rachitic bone. The bones seem to be so destitute of their resistance-capacity subsequent to probably faulty calcification, that they become frequently or easily broken. Green-stick fractures, therefore,are not infrequently found, and the bones generally affected are the radius, ulna , ribs, humerus, femur,fibula and clavicle.

Bone formation is carried on by the activities of the inner germinating cells of the periosteum. Smith[22] seemed to have expressed the most favorable statement regarding the role played by the periosteum in health as contrasted with its ~~outer~~ altered function in rickets. He says :

> "The growth of bone in thickness occurs from the under surface of the periosteum. In health, a soft, vascular, germinal tissue springs from the periosteal surface and rapidly receives lime salts, and is transformed into bone. This germinal tissue, consisting largely of capillaries arising from the fibrous tissue of the periosteum, is a very thin substratum, barely visible, transient, and constantly changing from its conversion into bone. .....In rickets, this vascular sub-periosteal tissue, not undergoing, or undergoing slowly or imperfectly, the osseous transformation, and, at the same time, increasing more rapidly than in health under the irritating influence of the rachitic disease, becomes a thick layer. Its color and appearance are like spleen pulp, so that the older observers supposed that there was a hemorrhagic extravasation between the periosteum and the bone. There is however, no extravasation of blood, unless it accidentally occurs from the numerous delicate capillaries. The resemblance to extravasated blood or spleen pulp is due to the abundant growth of large and thin-walled capillaries from the under-surface of the periosteum, as shown by the microscope. This vascular outgrowth is, for the most part, quite uniform over the diaphysis of the long bones ;while upon the cranial bones its thickness is much greater in one locality than another. The attempt at ossification also appears in this tissue. Lime salts are scantily or loosely deposited through it forming osteophytes--vascular and fragile--rather than true bones."

So that the periosteum is rather thickened and more vascular in rickets than normally, partly due to the thickened outer layer and partly to the proliferating, vascular,hyper-plastic, inner layer.

This pathological change of the periosteum seems to be responsible for the faulty , slow , imperfect, or even arrested ossification of the layer deposited on the bone. As a result, one may note a somewhat thickened but porous condition of the

outer portion of the shaft, although the inner layers may appear compact.

The X-ray examination, according to Findlay[3], not infrequently reveals a "homogeneous shadow devoid of all details. At times, however, the trabecular network is quite apparent but it is coarser, less regular,and more unevenly distributed than normal." On section of the long bone, one may note a more rapid absorption of the medullary layer and a more vascular appearance of the medullary canal than normally. These vascular changes or apparently hyperaemic conditions of the periosteum and of the medullary canal suggest some inflammatory process. In this connection, Cheadle[7] asserts:

> "This hyperplasia is generally regarded as the result of an inflammatory process , a view which is supported by the fact that with the subsidence of the active rachitic stage, more or less induration of the bone--sclerosis--follows."

Smith[22] upholds the latter view and that in the stage of re-construction which corresponds clinically with the convalescent period *of* the disease, there is produced a thicker and a firmer bone similar in process to the callous formation[22].He designated the condition as "osteo-sclerosis" or "eburnation" , rather than true ossification. The new-formed bone at this stage, according to him[22] , is more compact, stronger,and harder, although microscopically the elements of ~~the~~ true bone may be exhibited.

(1)(b) Chemical Pathology

The porous-like condition, flexibility, or brittleness of the bones is due to their insufficient content of calcium. Whether or not this deficiency of calcium results from an absorption of its mineral content from the already-formed bone, or from the lack of calcium in the food, or from the disturbed function of the periosteal layer or of the osteogenic cells so that the calcium even sufficient in amount is not properly utilized to form a true bone layer, is still a controversial question. But, in spite of Moore's[6] contention that the calcium salts in rachitic and non-rachitic bones present slight difference in quantity, there can be no doubt that in the rachitic bone, the proportion of the calcium to the organic content is much less than that in the normal. Smith[22] and Holt[26] both agree that, while normally the bone contains about one-third organic and two-third inorganic, in rickets the proportions are reversed and that "the chief loss is in the calcium"[26] Similarly, Osler[9] asserts :

> "The chemical analysis of rickety bones show a marked diminution in the calcareous salts, which may be as low as 25 or 35 per cent."

Moreover, Stoelzner[20], while discussing the pathological chemistry of rickets, says that the water content of the rachitic bones is higher than normal, and considers as the most important, the decrease in the mineral contents, especially the calcium and phos-

phoric acid.

(1) (c) The "Growing-Zone."

As has been remarked above, the region between the epiphysis and the diaphysis is enlarged corresponding with the beading at the junction of the rib and the cartilage. This change constitutes perhaps the most characteristic feature of the disease. It is more markedly noted in the regions of the ankle and of the wrist, where there is more strain, in the same manner as the largest beads may be observed in the lower ribs which move more freely during respiration; indeed, the lesion seems to be worse in the more actively growing parts of the skeleton , where the enlargement becomes responsible for the delay or even arrest in the normal growth or elongation of the bones. This is possibly due to the influence of certain factor or factors on the cells concerned in the process of ossification rendering them pathological in their function, so that the calcium is not properly absorbed, utilized, and converted, in the growing or proliferating zone into normal bone. The latter view may be, however, a subject for subsequent speculation.

Normally, the growing zone is represented as a straight, narrow, glistening, bluish-white line, sharply dividing the epiphysis from the diaphysis. In rickets, it is wider and thickened, occassionally ~~sometimes~~ five times the normal size[26] . It then appears as a

bluish cartilagenous area, somewhat softer than normal cartilage. On one side, this cartilagenous zone blends with the epiphysis and on the other, it sends tongue-like processes into the diaphysis. It contains scattered and irregular portions of uncalcified cartilages and bones surrounded by vascular spaces and connective tissues. Likewise, the epiphysis appears to be more vascular than normal and contains apparently enlarged but softer centers of ossification. This abnormal vascularity of the metaphysis and epiphysis again suggests that the process is inflammatory in character, similar to the finding in the periosteum and medullary canal of the diaphyssis.

There is then a subsequent enlargement of the growing end of the bone partly due to vascular proliferation in the enlarged growing zone and epiphysis. But whether or not this enlargement is largely due to hyperplasia of the cellular tissue at the growing portion or to the deficient absorption of the cartilage is still a debatable point. The widened transitional or proliferating zone termed as ~~as~~ the metaphysis consists histologically, besides cartilage cells, of blood vessels, of fibrous tissue, and of large amount of unossified bony trabeculae. The latter is known as the"osteoid tissue", and its presence in excess in the growing portion of the bone is the most important diagnostic feature of the disease. The osteoid tissues are not equally distributed; some are large, others may appear small. Normally,

the osteoid tissue, the development of which has been regarded as the first stage in bone-formation, rapidly absorbs calcium and becomes bone; so that under the microscope, it is represented as a very narrow, hardly perceptible layer, or it may entirely disappear.

It is interesting to contrast the process of ossification in the growing end of the rachitic and non-rachitic bone. In the normal bone, one observes under the microscope regularly arranged parallel rows of cartilage cells in the direction of the long axis of the bone. As these enlarge , they ultimately become confluent at certain portions to form the primary marrow spaces. The cartilage cells then undergo degeneration or become absorbed in the bone marrow. The blood vessels from the perichondrium shoot off branches accompanied by osteoblasts and connective tissue, which traverse the spaces at different levels but enter the bone perpendicularly to the long axis. These arterial capillaries, which vary in number according to the rate of growth, ramify in the primary marrow spaces but do not anastomose. The cartilaginous matrix or osteoid tissue becomes subsequently calcified , and so rapid is the ossification process, that normally it may be absent or appear only as a marrow rim under the microscope. In rickets, the proliferating cartilage cells do not apparently become absorbed rapidly, although the attempt of bone formation therein is apparently activated. As a result, one finds scattered groups of cartilage

cells and irregular islands of unossified bony trabeculae. The normal epiphyseal line is broken by the indentations or tongue-like projections of the bony trabeculae. Connective tissue is subsequently produced in this enlarged cartilagenous region. So that, as a whole, one finds in the metaphysis an abundance of osteoid tissue and large blood vessels with intervening connective tissue, all taking the place of the former cartilagenous matrix, which contain or enclose scattered groups of still unabsorbed cartilagenous cells.

(2) Soft Tissues.

Thus far, we have considered the bone changes which constitute the chief and characteristic lesions in rickets. They are more constant and distinctive than those of the soft tissues, although the latter may become invariably implicated or take an active part in the disease-process.

(2) (a) Muscles.

Whether or not there is a definite pathological lesion in the muscles, is still not settled. However, one may suppose that, as a result of deficient nutrition of the tissue and subsequent disuse, there may, later on, be a thinning of the muscles. This view is not against that upheld by Stolezner[20] and Holt[26] that there is a definite atrophy of the muscular elements. Jacobi[27] assures of a certain chemical change in the muscle fibre.

On the other hand, Moore[4] says that the rachitic muscle reacts normally to faradization[3]. Likewise Findlay claims that the electrical tests of muscles and nerves of rachitic individuals present normal readings. But, as a whole, considering the lack of correlation between the severity of locomotor symptoms and the extent of the osseous lesions, further studies on the histology and chemistry of the muscles and ligaments should be made.

(2) (d) Visceral Organs.

Now, just a word on the so-called "visceral rickets". We know that, subsequent to the contraction of the chest, the lungs may be rendered more vulnerable to infection and complication. There may, therefore, be lesions of bronchitis, bronchopneumonia, collapse of the lungs, and compensatory emphysema, etc. It is also probable that, due to the resistance of the pulmonary circulation resulting from the diminution of the respiratory field, a dilated right heart may not be an exceptional post-mortem finding.

Again, the contraction of the chest and probably of the diaphragm, tends to push the abdominal organs down; so that at autopsy, one may find the visceral organs displaced downward. But, whether or not there is a definite lesion in the liver and spleen, is still a matter of dispute. It is possible, as has been pointed out under Symptoms, that the normal liver may, due to downward displacement, appear clinically enlarged. This view

is not against the assertion of Fagge[5] that he has failed to find any lesion in the spleen, liver, and lymphatic glands whereas he found large, fleshy spleen in children free from rickets. Moreover, Turner[30] exhibited a case of an 18-year old child who died of an epileptiform attack with well-marked osseous lesion at the post-mortem table but without visceral changes. On the other hand, Dickinson[31] maintains that the enlargement of the viscera as spleen, liver, and even the lymphatic glands is an essential part of the disease as the changes in the bone. He[31] states that the lesion consists in the proliferation of the interstitial and epithelial elements. He further says that the earthy salt contents of the affected viscera are markedly diminished, contrary to the finding of Stolezner[20] who maintains that the soft tissues of rachitic children contain no less calcium than normally.

Goodhert[28] thinks that there are no sufficient evidences to warrant a statement that the liver is or is not diseased in rickets; still he supports the view that the spleen undergoes certain enlargement in the form of interstitial fibrosis. Jenner[17] seems to admit that there is an enlargement of the spleen and liver in rickets but the lesion, according to him, is not due to hypertrophy of the cells and fibrous structures, since such condition exists in other diseases distinct from those of rachitic enlargement. And Jacobi[37] points out that the tumefaction of the spleen may be often observed in rickets due to engorgement of the vessels resulting partly from the slackening of the circulation. Holt[26], on the other hand, opines that there are

no constant changes in these glands and that the latter may or may not be enlarged in rickets. This latter view may be more safe if we bear in mind that the enlargement in rickets may not have any connection with the disease at all. It cannot be held improbable that rickets may ~~not~~ superimpose upon syphilis in the same individual. In such cases, is the enlargement of the spleen and liver due to rickets or to syphilis ? Cheadle[7] thinks that "the enlargement of the lymphatic glands, liver and spleen, met with in some cases(of rickets) may prove to be rather a syphilitic than a rachitic origin". However, if we do admit that syphilitic splenomegally is more common, and that syphilis may exist in rachitic children, still there remains an impossibility to disprove the existence of an enlargement of the organ due to rickets alone. And again, although lesions may exist in these organs in rickets without appreciable enlargement and have escaped the notice of the clinicians, still it is equally possible that other diseases may have existed before or have superimposed upon the rickety condition, which may have been mainly responsible for the enlargement; and, it is not also unlikely that rickets produces a definite change in these glands modified by other undetermined conditions connected with the morbid process. Do all the pathological specimens of an uncomplicated rachitic spleen and liver show the same morphological picture ? And,

is this picture not present in complicated rickets or other diseases where rickets is absent ? As the question stands, a more elucidating work on the pathology of hepatic enlargement and splenomegally in rickets is needed before one is warranted in attempting to make a conclusive statement.

The gastro-intestinal disturbances in rickets point to some possible anatomical alteration. That there may be an atrophy of the muscular wall, would not contradict Jacobi's view[24] that the atony of the intestinal wall is responsible for th paresis and distension of the gastro-intestinal canal. Is the occasional diarrhoea met with in rickets due largely to metabolic faults ? Are there no other demonstrable lesions of the gastro-intestinal wall outside of possible atrophy of the muscular layer?

The changes of the brain and spinal cord have not ,as far as I am aware, been substantially described. The various occasional nervous symptoms, as above described, suggest possible lesions in the nervous system. The normal findings of electrical tests on the nerves[3] can hardly be taken as conclusive to invalidate whatever possible anatomical changes may there be to account for the irritability, restlessness, laryngismus stridulus, convulsions, tetany, etc. Are they purely reflex in nature or muscular in origin? If they be central, where is site of lesion?

Are they produced by some transient irritating influence acting on the nervous mechanism of the individual ? Or, are there lesions in the brain or spinal cordthat are still undemonstrable by our present pathological technique? Jenner[17] points out, as the cause of the enlargement of the head, the development of an abundant albumenoid substance in the white matter of the anterior lobes of the cerebral hemispheres. Is this all that can be demonstrated?

As far as I am aware, nothing is said regarding the pathological changes in the organs of internal secretion. It is certain that lesions have been found to occur in the endocrine glands of some of the experimental animals subjected to deficiency dietary; and it is not improbable that some similar changes may occur in rickets but not as yet determined. Is it only a disturbance of function in these glands without structural change that accounts partly for their abnormal role in contributing to the derangement of metabolism ? It seems, therefore, not a vain effort for anyone to make a more careful search and special study of the possible anatomical alterations of especially the adrenals and the thymus in rachitic cases.

II. What is Rickets ?

B. In Lower Animals.

1. Occurrence.

The concensus of opinion of most investigators is, that the disease "Rickets" exists ~~equally~~ in lower animals. To say the least, similar signs and morbid processes may be found in animals subjected to the same condition or conditions which we suppose to be responsible for the causation of the disease in man. For the lack of a better term, the so-called "Animal or Experimental Rickets"has been given to such a disease-syndrome in horses,sheep , dogs, cats, rats,lions,bears, monkeys, etc.

1. a. Etiology.

It has been claimed that the disease in lower animals rarely occurs spontaneously in nature unless they are kept under abnormal conditions. The morbid process has been found to result from two main causes: (1) effect of domestication, and (2) errors in diet.

The experience in Zoological Gardens regarding the inability of rearing young animals exemplifies not only the effects of diet but also of confinement. By taking away the animals from their natural abode and putting them in cages,

their freedom to enjoy the effects of exercise, air and sunlight, etc., is curtailed. It is obvious that the physical enjoyment of natural environmental conditions, contributes to the maintenance of well-being in all forms of life. It is possible, therefore, that by altering these conditions, the physiological balance of the individual may be disturbed. The importance of confinement as a cause of animal rickets is shown by Findlay[32] where he demonstrates that deficiency of fat or of any other dietary factor may produce marasmus in lower animals and not rickets; but by depriving the animal from exercise, even with liberal diet of milk and porridge, it becomes markedly rachitic. Likewise, Crisp[33], in discussing rickets in animals, expresses the view that the confinement and therefore the inability of the animals to get their natural food, gives rise to such morbid changes, viz; "impaired digestion, softening of the bones, enlargement of the ends, deficiency or maldistribution of the lime salts, weakness, distortions, and other symptoms as well known to attend rickets in human subjects".[33] He also points out that at the Regents' Park Gardens, a great number of young lions have been born but nearly all of them died before adult age; and then, he continues:

> "In private menageries, where the animals are moved about from place to place, a great number of lions have reached maturity."

Again, Dudgeon[34] asserts:

> "Young puppies and kittens born and bred in the animal houses attached to various scientific laboratories are especially liable to develop rickets, even when the diet has been most carefully regulated. This is mainly due to the difficulty of obtaining sufficient amount of light and air which is necessary for the animals."

Many such instances of the effects of domestication can be cited but whether or not the bone deformities ,which developed subsequent to the removal of the animal from its natural abode alone, were of true rachitic nature, can not be safely ascertained without other evidences. Moreover, it is conceivable, as is true in man, that similar bone deformities in lower animals are not exclusively found in only one disease. Nevertheless, there is no available reason at present to eliminate the possibility of some changes ~~referable to~~ simulating those of faulty nutrition brought about by other factors, which inevitably result from the exclusion of the animal from its normal dwelling.

The attempt to domesticate an animal deprives him not only of the enjoyment of his home life and freedom of his own action but also subjects him to a nutrition which may be detrimental to his physiological well-being.The famous experience of Bland-Sutton[35] in the Zoological Gardens, Regents' Park,London, seems to indicate that young lions, after the withdrawal of milk, and subjecting them to a diet of meat, bone,vegetables, and starchy materials, developed a morbid condition from which many had succumbed. If the disease which was then diagnosed as

rickets, could be prevented or overcome by the introduction of milk, or the addition of cod liver oil to the dietary without altering the environmental condition, it seems probable that something in the food was partly the responsible factor. An opinion may thus be formulated that the factor in question resides in particular constituents of the milk which could also be supplied by the cod liver oil, and seems to exert its effect on the nutritional mechanism of the animal. Although this hypothesis may not seem to be favorable to those who uphold the calcium deficiency theory, since the young lions could not masticate the bones given them from which the calcium supply could have been derived[32], still the work of Mellanby[19] on puppies, and more recently that of McCollum and his co-workers[36] on rats, have shown conclusively that the induced disease-syndrome termed "Experimental Rickets" is caused by a state of faulty nutrition of the rapidly growing animal and have advanced a view that some hypothetical substance is still to be sought for, by the lack of which in the diet, the disorder is apt to develop.

1. b. Diagnosis.

Granting that the disease "Rickets" may develop in animals, how can it be recognized ? In other words, what means are to be employed to establish a diagnosis? Cheadle[7] describes the physical signs in lion whelps by saying:

> "The condition is a true rachitis; there is the same feebleness of the muscles, the same debility, laxness of the sinews and bending of the bones; and the identity of the morbid changes has been fully established."

But the most concise and accurate description of the symptoms of animal rickets (puppies) seems to be that of Mellanby[37] found in the Special Report of the Medical Research Committee as follows:

> "The bones are defectively calcified and the legs bend, the ligaments are loose and emphasize the leg deformity. Swellings of the epiphysis of bones are obvious, the rosary developes at the costo-chondral junctions and other chest deformities according to the intensity of the affection. As in the rachitic child, the animals are lethargic and usually show great inability to run some time before the bone changes would prevent their so doing. That is to say, there is a loss of tone of the muscles often accompanied by a lack of desire to carry out physical exercise."

From the above description, one may infer that ~~very~~ there seems to be certain similarity of the physical signs of the disease in animals and rickets in the human subject. The premature decay or brittleness of the teeth may also be observed. Xerophthalmia may ~~also~~ be seen, although such a disorder has been regarded as possibly due to an entirely different factor from that causing rickets. McCollum and his co-workers[36] also point out the bulging of the abdomen, the downward displacement of the abdominal organs and the characteristic contraction of the chest, beside other osseous deformities, as guides in establishing a diagnosis.

The beading of the ribs does not, however, seem to be pathognomonic as such enlargements may likewise be seen in scurvy[8] and possibly in other deficiency diseases[21]; unless, of course, it can be shown that, with the latter, rickets might not be coexisting.

The bone lesions, which, as in men, present distinctive features, are of diagnostic value. In the Special Report of the Medical Research Committee[37] the following statements are found:

> "After death the calcium content of the bones is low and the structure as revealed by histological examination of the bones, is characteristic and pathognomonic, the irregularity of the epiphyseal cartilages and the presence of osteoid tissue in abundance being the most marked features."[36]

Besides the above leaions, McCollum and his co-workers add the following as diagnostic signs of experimental rickets:

> "1. The presence of a widened transitional zone,
> 2. A more or less increased width of the cartilage and a greater or lesser irregularity of its shaftward margin as the result of the invasion of the epiphysis by the diaphyseal elements."

And, it is possible that such changes may differ in degree according to the type and kind of diets[36], and probably to the particular susceptibility of the animal or of the species, since it has been remarked that the more rapidly growing the animal, the more abundant is the formation of osteoid tissue.[32]

2. Similarity to Human Rickets.

Now we are confronted with a somewhat delicate question: Is the disease induced in lower animals the same as that in man?

It is obvious that individual reactions of animals of the same or of different species to a common stimulus widely differ In other words, the same factor or factors that cause a definite pathological change in man may produce a different lesion in lower animals. The veracity of this statement may not be doubted, when we come to consider that, while polished rice may cause the disease "beri-beri" in man where, besides the characteristic lesions, there may be hypertrophy of the right heart without appreciable lesions in the adrenals outside of simple congestion, the same type of deficient dietary produces in pigeons, as experimented by McCarrison[38], a distinct atrophy of the heart and a marked hypertrophy of the suprarenal glands. And even if it were possible to demonstrate the disease "rickets" as one and the same in lower animals and human subjects, still the degree of lesions may again differ, as it is possible that experimental animals such as rats, may be more susceptible to it than man.[8] Moreover, there seems to be a considerable dispute as to the identity of the histological findings of the rachitic human bones and those of the lower animals. Stoelzner[20] and Holt[26] express similar opinion on this matter. They believe that ricket-like condition of the bones of growing animals may be produced experimentally by subjecting them to a diet deficient in calcium and phosphorus but histological examination of the osseous lesions are, by no means, identical with that of human

rickety bone. The resulting lesion in the experimental animal is, according to them,[20&26] in the nature of pseudo-rachitic osteoporosis which may be, unlike human rickets, improved by the administration of calcium salts alone.[26]

There seems to be some danger, therefore, of establishing a diagnosis of rickets in lowef animals from the macroscopic changes presented by the animal body under ~~the~~ dietetic experiments even if the identity of the disease in both species may be admitted a priori.From a critical standpoint, Findlay[32] upholds the view by saying:

> "Careful microscopic examination has demonstrated two facts, viz:
> 1. That all examples of spontaneous experimental rickets in animals described by veterinarians and experimentalists are not identical with the disease as met with in man; and
> 2. That merely naked eye or chemical examination of the skeleton (as pointed out by Schmorl) has been the cause of a great deal of misconception in the subject."

Now, where do we stand? Is there or is there not such a thing as experimental rickets? And, if so, is the morbid process identical with that in man? Although we do admit that there may be osseous lesions in animals subsequently produced by a deficient dietary or by domestication or by some other factors which do not seem to be homologous to the morbid findings in man,[20 &26] still we are not justified in concluding positively that, with similar physical signs and pathological lesions, the disease in animals is not rickets. It is noteworthy

that our experimental research workers are fully aware of their results, being guided by tests and other means in the accurate recognition of the disease in lower animals so that full confidence on our part may not be undesirable. In other words ~~Moreover~~, if we bear in mind that the morbid process may be induced in experimental animals by almost identical factors under which the disease may develop in man and that the similarity of the morbid signs and lesions resulting therefrom may be established in both species, the possibility of their being one and the same disease may be carried farther away from the shadow of doubt.

The burden of proof is not only confined in the similarity of the etiological and pathological aspects of the two conditions in both species, but also in their reaction toward therapeutic agents. The specificity of cod liver oil in the curative treatment of the disease in man is conclusively admitted by practitioners and experimenters, although it may be possible that in some cases, the oil exerts a retarded or negative influence.[4]

Its prophylactic value is also established beyond doubt. In this connection, Hess and Unger[39] have shown statistically the beneficial effect of the oil on the disease among the negro children in Columbus Hill District of New York City. The following Table which may not be out of place to reproduce, illustrates

some of their results:

"Comparative Incidence of Rickets Among Infants Receiving and Not Receiving the Prophylactic Therapy"

	Duration of therapy month	No. of Infants	Infants not developing rickets	Infants developing rickets	% Non-rachitic
il given average total) 54 oz.	6	32	30	2	93
il given Average total) 23 oz.	6	5	4	1	80
il given average total) 21 oz.	4	12	7	5	58
il not given	--	16	1	15	6 "

he conclusion from the above Table is therefore obvious. This remarkable therapeutic and prophylactic effect of codliver oil on human rickets deserve an important consideration from an administrative public health point of vie

In animals, similar effects of the oil may be observed. his is clearly shown by the exhuastive works of Shipley, Park, ~~and~~ McCollum nd their co-workers[36] on the effect of cod liver oil on rats with experiment-l rickets where, they say,:

> "The results of this series of preliminary experiments are twofold: They afford ocular and conclusive evidence of the specific beneficial effect of cod liver oil on rats suffering with experimental rickets in that some substance or substances in the oil cause calcium to be deposited in the same fashion in which deposition occurs in spontaneous healing of rachitis in man. Moreover, they prepare the way for the elaboration of a new test, which it is hoped may eventually prove even to be roughly quantitative for the determination of the calcium-depositing potentiality of any substance in terms of cod liver oil units."

The experience of Bland-Sutton, which has been before referred to, may here be reaclled. There may therefore, as McCollum and his co-workers express,[36] be conceived a substance or substances in the milk or cod liver oil which are concerned not only in the etiology but also in the therapy of the disease both in man and in animals. The experiments of Mellanby[19] are not opposed to this view. This so-far undetermined "food accessory" substance, which will again be referred to, has been termed the anti-rachitic factor.

Taking into account the foregoing facts, since the morbid process in lower animals may be shown etiologically, pathologically, and therapeutically identical with that in man, one may not be safely justified in doubting that in animals, there is a disorder called "experimental rickets" corresponding or homologous to the human type, in the same category as "polyneuritis gallinarum" in fowls to "beri-beri" in man.

III. ETIOLOGY.

The causative factors that seem to operate in the development of the disease are apparently so numerous that, for the sake of convenience, they may be grouped under two sub-headings:

A. The Pre-Disposing, and B. The Determining.

A. predisposing Causes.

1. Geographical Distribution and Climatology.

Historically, the disease is said to have been so prevalent throughout England at about the time of its recognition, that it received the name "Morbus Anglicus." But it was found out that England was not its only home.

Rickets exists in all quarters of the globe. In Europe and North America, it is more abundantly distributed in the region within the temperate zone. It is believed that the disease rarely occurs in North Greenland and Faroe Islands; and it occupies a subordinate place in the morbidity statistics of Iceland, Norway and Denmark. According to Palm[40], Hirsch and Creighton[2],

> "Its principal seats are Germany, England, Poland, Belgium, France, and Northern Italy; while southern Italy, the southern provinces of Spain and still more, Turkey and Greece, enjoy a notable immunity from it."

Although the disease exists in the United States, it

is not so abundantly ~~established~~ scattered as in the European countries. Indeed, it seems to be more or less limited in such large cities as New York, Philadelphia, Cincinnati and Baltimore.[2] Rickets is less common or rare in Syria, Arabia, India, Java, Cochin-China, China, Japan, Madagascar, Mayotte and other Pacific islands, Egypt, Algeria, Senegambia, California, west coast of Mexico, the West Indies, Guiana, Buenos Aires, and Paraguay. Palm[40] and Watson[41] agree that the abundant sunlight, ventilation, lactation, and the special food that the natives of India eat, explain the relative immunity of the population of that country. The same explanation (relative to sunlight and ventilation) may be offered as to the rarity of the disease in China. Cheadle[7] thinks that the consumption of a large amount of fish oils in Japan and the late weaning of Japanese children (sometimes up to five years old) prevent the people from developing the disease. On the other hand, it is said[32] that some cases of rickets have been found among the recruits examined by Ogata in the Province of Toyama, Japan, on the western shore of the northern island ; and Findlay[32] believes that in this region the disease, which has been, according to folk lore, existing endemically for at least fifty to one hundred years, was due to the poor light and improper ventilation of the houses, exceptional to the rest of Japan.

From the above remarks, it may be inferred that rickets seems to exist in all parts of the world. However, its occurrence may be influenced by climatic conditions, notably with regard to altitude, temperature, sunlight, and humidity.[1] It is said that the disease is rare at high elevations "especially when the soil is dry". With reference to th relation of rickets to climate, Hirsch and Creighton[2] give the following statement:

> ".....the disease in any form, and particularly in its severe forms is much rarer in tropical and sub-tropical countries than in high altitudes; but in amount and severity of type, it stands in a definite relation to climate that countries with a cold and wet climate, subject to frequent changes of the weather, such as Holland, many parts of England, the North German plain, the mountainous regions of Central and Southern Germany, and the plains and mountainous districts of Northern Italy, if they are not the exclusive seats of rickets, are at all events, its headquarters."

In certain regions of the countries above mentioned, wherever the nature of the soil has a good deal to do with the character of the climate, the disease seems to be worse. Such places are, according to them[2] :

> ".....in the wet plains of Lombardy, of Alsace, of Holland, of Belgium and of North Germany; as well as in valleys, deeply cleft and traversed by many water sources, of the giant Mountains, the Thuringian forests, the mountainous parks of South and Western Germany, and the Alpine foot hills of Austria and Northern Italy. On the other hand, at high elevations, and on dry soil within those regions, rickets is of comparatively rare occurrence : as at the highest places in the Erzgebirge, and in the Norican Alps, although the conditions of living among the people are, in many respects, unfavorable."

It is not at all improbable, that rickets has not been receiving the proper attention that it deserves. In other words, it is possible, that in places where rickets is said to have been absent, the careful search for the disease may have been lacking; and it is not unlikely that quite a number of cases may have escaped notice in places where it does not occur. It may therefore be inferred that its exact geographical distribution is not as yet determined; and if it be true that the malady accompanies the path of civilization, we would expect that its distribution would keep on changing with the progress of time ~~and~~ as well as with the changes of climatic conditions.

2. Frequency and Season Occurrence.

Rickets seems to be now more frequent than it formerly was. Whether or not **this** is due to a more adequate diagnosis or to the actual increase of the number of cases, is not known. Findlay[3] does not believe that there are available figures, by which one may judge the relative frequency of the disease in the general population of different districts, since the statistical data published, refer only to the prevalence of the disease in hospitals and other institutions. Barlow and Bury[1], however, express that the disease is more frequent in such densely populated cities as Prague, London, and Manchester where an average of 30% of the young children attending the hospital have been affected

by it. The disease is also prevalent in Liverpool, Glasgow, Vienna and New York, and in the manufacturing districts of[7] Lancashire and Yorkshire, the Black County, Scotland and Wales, where the poor class is especially affected. Hirsch and Creighto give some statistical data, which are hereby tabulated to illustrate the percentage proportion of the disease in certain cities

Statistical Calculations on the Proportion of Rickety Children among Certain Totals of Patients below Five Years of Age.

Cities	No. of years of observations	Places or Institutions	Percentage
Copenhagen	6 years	Children's Hospital	8.4%
Basle	6 years	Outpatients	15.0
Dresden	20 years	Children's Hospital	20.0
Berlin	10 years	(Charité (Outpatients	25.0
Frankfort-on-Main	(in 1881)	Christ's Hospital for Children Outpatients	25.0
"	(in 1882)	do	28.0
"	(in 1883)	do.	27.0
Philadelphia	-----	Outpatients	28.0
London	Several years	St. Bartholomew's Hospital	30.3
Manchester	-----	Outpatients	30.3
Prague	2 years	the Polyclinic	31.1

Stoelzner[20] considers rickets as an extraordinarily widespread disease where it affects 90% or more of the poor children of great cities. He also affirms that rickets is rare among the yellow race and that "the negro children in the tropics may remain practically exempt but those in regions in which it is endemic seldom escape." Osler[9] asserts that 50% to 80% of all the children at the clinics of London and Vienna present signs of rickets. He[9] also says:-

> "In the cities of the United States, it is very prevalent, particularly among the children of the negro and of the Italian races."

In an infant asylum, Hess and Unger[8] found that more than 90% of the infants showed some signs of rickets; and Mellanby[19] asserts that, according to Schmorl's histological investigations, 90% of the children who died before four years old, had had rickets.

The disease seems to be worse in winter than in summer months and this difference is more noticeable among the poor.[1] Cheadle[7] says that there are more cases in the cold winter months when the children are, most of the time, confined indoors, destitute of light and fresh air. Likewise, Holt[26] affirms the view that the symptoms of rickets are more severe in the winter and spring, although the statistics from the four large out-patient clinics show that there were more than twice the number of rachitic patients treated from January to June than from July to December. Findlay[3] supports similar opinion , namely, that cases

of rickets become especially numerous during the spring months and diminish during fall. And regarding this seasonal variation, Holt[26] says: :

> "What is it that determines this we are as yet quite unable to say."

However, we may be justified in the belief that the seasonal variations may partly modify the course of the disease and probably may predispose the development of the lesions in susceptible individuals.

3. a. Age Incidence.

Rickets may be regarded as a disease of early childhood, generally within the first two years of life. At what particular age, the signs and symptoms generally appear, is a matter of speculation. The following aggregate statistical figures, as quoted by Smith[22], may give roughly the optimum age at which the malady may develop:

	No.of cases
"Duringthe first year............	99
" " the second half of first year,..........	259
" " " " year	342
" " " third year,.........................	134
" " " fourth year	31
" " " fifth year	17
" " " fifth and ninth year,................	21
Aggregate.....................	903"

From the foregoing Table, it may be inferred that children between the age of six months to the end of the second year are more prone to manifest the disease clinically. This is not against the view expressed by Osler[9] that the disease occurs within the first and second years of life but rarely manifests itself before the sixth month. Moore[4], however, says that out of 1053 cases examined, the earliest age at which rickets was seen, was ten weeks, and the latest seemed to have begun at the 20th month of life; although Barlow and Bury[1], on the other hand, claim that rickety rosary may be identified clinically as early as one month of post-natal life, and pathologically beads have been found on dissection of stillborn child.

The last view brings us up to the question of intra-uterine rickets. Is the development of the so-called foetal rickets possible? Barlow and his co-worker[1] answered the question by assuming that the disease develops in utero as an exaggeration of the normal process.[1] They describe the lesions of the intra-uterine rickets as bending of the bones; repaired, annular, intra-uterine fracture; beading of the ribs; delayed ossification of the membrane bones of the cranium; broad-cushion of proliferating cartilages; etc. Likewise, Shattock[42] gives a more lengthy and accurate description of the gross osseous lesions of what he claimed to be rickets found in the foetus, but fails to differentiate the condition from that of cretinism.

Fagge[5] goes so far in the assertion that rickets may possibly develop even in the first-setting-in of the process of ossification within the foetus. Cheadle[7] and Smith[22] confirm the existence of foetal rickets; the development of which in utero has been regarded[43] as the influence of the defective nutritional condition of the maternal blood. On the other hand, it is not impossible to assume that, foetal rickets might not be developed in mother's uterus even she exhibits tendency to procreate children susceptible to the disease.[16] Moreover, Stoelzner[20] and Baxter[44] both agree that the so-called foetal rickets is not identical with the true rickets; and Holt[26] gives the following remark:

> "More careful clinical observation and especially pathological studies have shown, however, that evidences of rickets are not found at birth. There is probably no such condition as foetal rickets."

While it may be questionable, therefore, whether or not foetal rickets exists, there seems to be no doubt that the clinical manifestation of the disease may not appear until late in life. An interesting living case is cited by Dewitt[45] where the boy has been healthy after nine years of age; there was no history of syphilis in the family; parents, brothers, and sisters were healthy; he has been living in sanitary condition and had plenty of outdoor games; the only defect in the life history of the boy was that he was weaned at two months old; and it was not until nine years and thee months after, when he

he began to show signs of rickets. The diagnosis was confirmed by a committee especially appointed to examine the case, who excluded other possibilities ; but the curious thing about the disease is that it could not be arrested or alleviated by cod liver oil, but by potassium iodide. Barlow[1] and his co-worker cite two cases where active manifestations came at eleven years of age, which proved to be rachitic by post-mortem examination, but they believe that they were recrudescence rather than new development of the disease. However, Holt[26] asserts that although rare, late rickets may occur in children between six to twelve years, while Stoelzner[20] claims that specific rachitic lesions may manifest themselves clinically as late as the age of puberty. It may be inferred therefore that, while the disease may develop from birth until probably at the age of puberty, the age at which the child is most predisposed, may be safely stated to be from six months to two years; in other words, this age may be taken as the most dangerous to the growing infant as far as rickets is concerned.

3 b. Sex Incidence and Racial Predisposition.

Sex seems to exert no influence in the development of the disease, since the male and the female children are equally affected. This view is upheld by Cheadle[7], Osler[9], and Holt[26] and others, although Fergusson[25] in her extensive statistical work,

concludes that rickets is slightly more prevalent among the males than among the females.

The unusual prevalence of the disease among the negroes and Italians[9] over the other races in New York City has been previously remarked upon. In this connection, Holt[26] offers the following statements:

> "So far as our observations are concerned, there is no peculiarity in the food of these people which explains the prevalence of rickets among them, and it must be attributed to a race peculiarity."

Hess and Unger[8] make similar but rather reserved remarks by saying that the prevalence of the disease among the negro infants, who are living side by side with the whites, obtaining the same milk supply, is indicative of other important influences in addition to the food. How does this racial peculiarity work to bring about the development of rickets?

4. Heredity and Diathesis.

Whether or not heredity plays a role in the development of the disease is an open question. Congenital rickets may be possible, but the existence of hereditary rickets remains still not far from the shadows of doubt until the transmission of the disease through one or both of the parental cells --spermatozoon or ovum --is conclusively demonstrable. Opinion on this matter is divided. Parker[13] emphatically asserts his belief that rickets is constantly congenital and that heredity plays a very

important role in the etiology of the disease. Holt[26] on the other hand, expresses :

> "There seems to be no greater reason for denying the influence of heredity in rickets than there is in arterio-sclerosis or tuberculosis."

From an etiological viewpoint, therefore, we cannot soundly admit that heredity per se plays an important part in the direct causation of rickets since we do not have proofs to show that the causative factor, whatever it is, is transmitted from the parents to the offsprings through the primary germinal cells.[9] If hereditary rickets, as having originated from the parents, is warranted because either the father or mother or both, had had rickets in their childhood, we would be denying the fallacy that measles, scarlet fever, and typhoid fever may be also hereditary diseases. However, even though the theory of hereditary transmission of rickets does not appear to us convincing, still it may be conceivable that the condition of the health of the mother during pregnancy, as a significant factor in preparing a rachitic field in the body of the child formed in her womb, can not be entirely eliminated. Barlow and Bury's[1] assertion, that the later children of a large family are more liable to be rickety and that this phenomenon exists generally among the poor, seems to be confirmatory to the above opinion ; for then it would be conceivable that the repeated pregnancies of the mother may presumably tend to decrease the nutritional-giving capacity of her blood subsequent

to her weakened vitality. This view seems to receive the support of Cheadle[7] who says:

> "The influence of heredity is probably limited to the transmission of a weakly constitution, or to some factor of imperfect nutrition of the foetus in the womb."

But he further says[7] :

> "....that children of perfectly healthy persons become rickety ; in vast majority of cases, indeed, rickety children are born of parents who do not exhibit the smallest trace of past rickets."

The question of individual predisposition, then, seems to deserve some attention. Is there or is there no diathesis in rickets? Besides what is above stated, some writers[43] consider rachitic diathesis in the same category as tubercular, soorbutic, gouty, or leprous diathesis, and that the degree of the derangement of digestion or metabolism producing the disorder may be influenced by the idiosyncrasy of the individual. This is corroborated by Hirsch and Creighton[2] who point out that the disorder of nutrition is secondary to the effect of morbid diathesis born with the child, contrary to the opinion of Longhurst[46] and Lucas[14] who consider that the disease is due to imperfect nutrition and results from the evils of civilization alone and not to diathesis. Stolezner[20] gives the following remarks:

> "If this hereditary predisposition is absent , children often remain free from the disease even if fed artifically."

It may safely be concluded therefore, that, although the direct transmission of the disease from parents to offspring lacks confirmation, still the rickety diathesis seems to have some stability and support to explain some of the unknown facts connected with the disease. For instance, it is a fact that the reaction caused by the unknown specific causative agent differs according to the individual, and, this peculiarity of reaction seeks for its explanation mainly in the degree of susceptibility or, in terms of morbid conditions, the difference of diathesis. In other words, the extent and possibly the setting-up of the rachitic lesion may be in part a measure of resistant power or constitutional predisposition to this particular malady.

4. (1) & (2) Parental Influence.

Contrary to the opinion of some [3], acquired predisposition to rickets in certain individuals may be considered as a contributory factor but not the direct causative agent of the disease. How is this diathesis produced? The question seems to be partly answered by Smith [22] when he says:

> "In some infants there is an undoubted hereditary predisposition to rachitis. Feeble digestion and defective assimilation in the infant, which are, (as we shall see) important factors in producing the rachitic state, are often traceable to diseases or cachexia of one or both parents. The offspring of a tubercular, syphilitic or otherwise eneefbled parents, is more likely to become rachitic than those of healthy and robust ancestry; and it appears that disease of the mother is more apt to entail a rachitic predisposition

> than that of the father. Amongthe parental causes may be mentioned poverty, hardships and defective nutrition of either parent; age of the father, and exhaustive discharges of the mother such as purulent, hemorrhoidal, or uterine fluxes."

To have a clear understanding of the parental influences in predisposing the child to rickets, the social and economic conditions are to be considered with the health and habits of the father and mother. In a way, the health and habits of the parents may be largely influenced by the condition under which they live and this is determined by, outside of educational training, their social and economic status. It may be expected that in the well-to-do class, the number of rachitic cases should be less. This is confirmed by th finding of Fergusson[25] among her Glasgow cases, namely, that although living in the same district, the social conditions of the non-rachitic family are better than those of the rachitic . The well-to-do families, therefore, are not exempted from the disease; indeed, it may be as frequent and sometimes even more[16] among them although possibly milder,[1] as among the poor, especially if disregard or neglect is given to the hygienic requirements of the young children , particularly with regard to the use of improper food.[22] On the other hand, O'Donovan[47] from his clinical experience among the negro children in the "Black District" of Baltimore, states that he has seen no rickets even in the poorest and worst conditions of lodging quarters where the children were suckled by their mothers; but

that rachitic children were found in the better-house surrounding where improper alimentation has been given. While this statement may be true, still it seems quite dangerous to construe that the lack of breast feeding is a factor in the causation of rickets, since it may be shown that artificial food may be as nutritious as human milk. This question will again be referred to later.

It has been said[14] that the oldest child of the rich and the younger children of the poor are the ones most likely to be affected. In this connection, Lucas[14] states :

> "The oldest child of the rich suffers because it is an experimental child, and the parents learn by practising on it how best to feed those which follow... .....The younger children of the poor suffer because, with large families, the parents are unable to supply sufficient food for them."

Fergusson[25] holds that the probability of rickety development increases with the number of children in the family. It may be interesting to note in this connection that Baxter[44] in the investigation of one hundred rachitic children, states:

> "A larger proportion of the above cases can hardly be ascribed to the influences of repeated pregnancies in exhausting the mother's health or reducing the standard of material comfort enjoyed by the parents."

This statement, however, cannot invalidate the opinion held by Osler[9] in that, rapidly repeated pregnancies and prolonged lactation, especially during gestation period, are accessory etological factors in some cases. And among the conclusions drawn by Fergusson[25] in her exhaustive statistical studies on the social and economic factors in the causation of rickets as far

as the health and habits of the parents are concerned, she says:

> "1. Whether the parents are country or town bred, has no influence on the incidence of rickets in the children.
> 2. The state of health of the mother is only a contributory factor in the development of rickets in the child in so far as it affects maternal care, or is an index of the conditions under which the child lives.
> 3. The habits of the mother and the care taken of the children have a marked effect.
> 4. The health and habits of the father only act by modifying the social conditions under which the children are reared."

The occupation of the father should also be considered especially if his wages are low. It is obvious that, if his earning is not sufficient to meet the demands of a sanitary home life or if he is weak to earn a living, the mother shares in the evil consequences. In this connection, Fagge[5] remarks:

> "The illness of a laboring man may deprive his wife of nourishment, throw heavy work upon her, and in many different ways, render her likely to bear weakly infants; it may prevent the children from receiving proper food, may interfere with their being taken out into the open air, may confine them in a small and cramped rooms,and mat limit their supply of warm clothes."

So, whatever bad influences act on the mother's health, may possibly diminish her nourishing capacity which may either directly or indirectly in turn contribute partly in the development of disorders of nutrition of her future children. This view seems to agree with that of Jenner[15] when he says:

> "The health of the mother, however, has a decided influence on the development of rickets in the child. Whatever renders her delicate, depresses her powers of forming good blood, that tends to produce rickets in an offspring."

5. Hygienic Environment.

There is no doubt that defective hygienic condition may contribute partly to the causation of rickets in susceptible individuals. This assertion is supported by prominent writers on the subject. However, the possibility of the disease developing in the most sanitary condition but defective in other factors, cannot be denied.[7]

5.a. Overcrowding.

It has been previously remarked upon[1&7] that, in the smoky, industrial, and densely populated cities of London, Manchester, Liverpool, Glasgow, Vienna, Prague and New York City, the disease is more or less prevalent. It is obvious that in these cities, the crowding of the population of probably mixed races, especially of the poorer class, not only favors the dissemination of contagious diseases, if any, but also influences in the building up of an insanitary surrounding where the air becomes impure, light insufficient, food unsound, etc.--all tending to diminish the vitality of both parents and children, and rendering them susceptible to diseases of all sorts to which they are predisposed. It is not unlikely, therefore,

to find more cases of rickets in such districts although it is possible that in the above places, other factors may play and that the latter may be more important than the faulty hygienic surroundings as a factor. The significance of the effect of climate should also not be neglected in this connection.

5.b. Domestication.

The "theory of domestication" of von Hannsemann[48] is one of the most famous from a historical point of view. It has been offered to explain the liability of negroes to develop the disease when brought to civilized communities, when in their natural, wild, African homes, they seem to be exempt from it.[20] It may partly explain the occasional prevalence of rickets in city infant asylums, except those of New York where greater attention is given to sanitary condition.[22] Of course, in the institutions above mentioned, one should not neglect the kind of food that the children eat. Confinement has been considered as one of the factors that lead to the production and prevalence of the disease in the poor tenement houses of large industrial cities, where the children have less chance to enjoy the effects of physical exercise, healthy surroundings, personal cleanliness, bright sunlight, pure air, and balanced food. Rickets has been found to develop chiefly among the foreign elements confined in dispensaries and hospitals of large cities.[26] Findlay[32]

lays stress on the importance of the lack of physical exercise during confinement and he proved experimentally upon pups that by depriving the animals of exercise, even if the surroundings were normal and diet of milk and porridge liberal, rachitic lesions in the bones were produced. His experiments were checked by control animals; and he offers, as a possible explanation in the inducement of the rickety condition in these cases, that the deficient exercise may hinder the utilization of the food and favor the production of waste products. This statement however, needs confirmation.

Again, the theory of domestication has been applied to the inability of rearing young animals in zoological gardens, where they were confined in cages removed from their wild natural abode. Similarly, it should be recalled that young puppies and kittens born and bred in animal houses, and other scientific laboratories develop rickets, even when they are fed carefully with nutritious diet.[34] The resulting lesions, however, in these cases, are quite questionable for they had not been shown histologically whether or not they were rachitic; or if so, whether or not no other possible factors were responsible for the condition. Furthermore, in the Special Report of the Medical Research Committee[37], it is stated :

> "In E.Mellanby's experiment, puppies developed no signs of rickets during confinement for three months when fed on adequate diets."

However, the value of the application of the theory in man, is not as yet definitely ascertained. Confinement per se, so as to exclude the beneficial effects of exercise and outdoor life, obviously disturbs the normal mechanism of the body and not unlikely that concerned in the proper metabolism tending to give rise to nutritional disorders.

The unsanitary condition of the dwelling is perhaps just as significant as the lack of exercise. The effects of unhygienic surrounding have been alluded to and may account for the prevalence of rickets among families living in the crowded tenement houses of great cities.[22] Poverty obviously leads to the development of unsanitary homes, and rickets is not uncommon among poverty-stricken families. However, this must not be taken to mean that the sanitary abode of the rich does not welcome the spontaneous appearance of rachitic guests. But, if personal cleanliness is one of the pre-requisites of health maintenance, it should not be absurd then to state that such disease as rickets may develop more rapidly in individuals neglectful of hygienic requirements. These views do not seem to disagree with the studies of Fergusson[25] who, in her comclusions regarding the influence of home sanitation in the development of the disease, says:

> "21. The district of the city on which the child dwells has not so great an influence in the developments of rickets as the actual condition of the home.
> 22. The average number of persons per room was almost one person more in the rachitic than in the non-rachitic families.
> 23. The cubic space per person was 32% less in families with cases of marked rickets than in families who were ffee from the disease.
>
> 24. The cleanliness ofthe house was distinctly better in the non-rachitic than in the rachitic family. "

True as these results may be, for they were based on a painstaking statistical study, still it seems perhaps dangerous to regard domestic hygiene as the sole responsible factor in the causation of the disease. That it may, either difectly or indirectly, contribute to or exert an influence on the real yet undetermined causative agent of the disorder, seems to be a more tenable hypothesis.

The sanitation of the home is determined, not only by its cleanliness and its space allotment per capita, but also by the amount of light and ventilation it receives. It is generally accepted that air and sunlight are essential for physiological existence and well-being; and it is not unlikely a potent factor in bringing about a healthy nutrition in a growing animal.[16] In thickly populated sections, where the air is not as pure and sunlight not as bright, nutritional disorders may not infrequently be liable to occur. This notion seems to receive the support of Findlay[32] :

> ".....that children living in top-flat houses, being probably ~~being~~ taken out little, were more prone to the disease (rickets) than those occupying houses on the ground level."

[32] He believes that confinement and deficient fresh air make the child more lethargic and that perhaps the subsequent deficient oxygenation of the blood helps toward the production of the special rachitic metabolic error. And in his conclusion, he says:

> "In view of these facts--the effect of deficient exercise on the calcium retention, the influence of confinement in the production of human and experimental rickets, and the frequency with which the disease is encountered in overcrowded houses--I consider it not unlikely that rickets would be exceedingly prevalent in those parts of the world where the people are confined in the badly ventilated houses and where sunlight was absent for long periods of the year."

According to him, the consumption of more fats, during winter, explains the absence of the disease in the northern countries around the arctic region (Iceland,Greenland,and Alaska), although the people are confined for most of the time in the badly ventilated huts. He also explains the bandy-legged deformities encountered in the Esquimos as probably due to the lowness of their houses, the heavy boots they wear, and their being crouched up for most of the time in their boats.

The significance of air and sunlight may not be well appreciated without taking into account the works of older writers. Barlow and his co-worker[1] says:

> "The evidence is indeed abundant as regards both animal and human rickets, that impure air,

> "is one of its most fertile causes, and we think that it accounts largely for the geographical distribution of the disease....Want of sunlight is also a potent factor in the causation of the disease."

Similarly, Hirsch and Creighton[2] remark:

> "A good deal more important for the origin of rickets than improper food is the effect produced upon the organism of the child when it is kept continuously in a badly ventilated and crowded apartment, where the air is saturated with moisture and tainted with products of organic decomposition."

The rarity or absence of the disease in tropical and sub-tropical countries, where the people enjoy outdoor life with plenty of fresh air and sunlight, may strengthen the above opinion. Palm,[16] after an exhaustive and painstaking study of the absence of rickets among the natives of China, India, Morocco, and Japan, states that sunlight is the most important element in the etiology of the disease. From a critical point of view, he says that it is not a disease of poverty, for, Great Britain is one of the wealthiest nations of the world and yet rickets abounds, while India is one of the poorest countries in the world and yet enjoys a practical immunity from it. Rickets, according to him,[16] is not due to deficient sanitation for England pays more attention to and spends more more money for sanitation than any other country, while countries neglectful of ordinary hygienic precautions, though they pay the penalty in other ways, are not scourged by the disease. He also regards rickets as not due to deficient

food since the wives and children of the working class of England are better fed than the teeming population of China and India whose staple diet consists mostly of rice and vegetables. Moreover, the English town-bred rickety child and its mother are, as a rule, better nourished than the healthy child and wife of the farmer, and by the process of exclusion[16] he arrived at this point:

> "...The most salient fact with regard to the climate of these countries which enjoy immunity from rickets is the abundant sunshine and clear skies. On the other hand, the feature of our British climate, which is most striking to anyone who has lived for some years in the East, is the want of sunshine and the dull grey skies or frequent fogs."

The lack of sunshine in the narrow alleys, where the children of the poor play, may explain the abundance of rachitic victims. Moreover, the children of the poor may be more liable to develop rickets because the mothers cannot afford to send them to the fresh air and sunshine, their time being taken up with domestic works. And, in comparing the morbid processes subsequent to the effect of excessive or deficient light on the functional activity of the man and the plant, ~~he~~ Palm[16] says:

> "A further analogy between the plant and animal may be found in the fact that while the light is essential to the well-being of the growing organism, the exclusion of light is the condition of development of the same organism in its embryonic stage. Deficiency of light after the embryonic stage is passed, and when nutrition depends upon the chemical changes which are due to exposure to light and air, leads in the plant not only to general malnutrution, but to excessive growth of the internodes of the plant and deficient growth of leaves. This is, presumably, a partial continuance of the embryonic mode of growth under the partial continuance of the embryonic

> "condition, darkness. Similarly, if the animal at a stage when it is fitted to grow and thrive in the air and light, should light be more or less excluded, we should expect ill effects to follow of the nature of a partial return to an embryonic mode of growth. It is significant and suggestive that the striking point in the morbid appearance of rickets is the continued growth of the embryonic cartilage instead of its conversion into bone. It suggests the query whether we have not here the homologue of the excessive growth of the internodes of plants when kept in comparative darkness, and whether we ought not to regard rickets as a conversion to an embryonic type of nutrition."

The above quotation suggests a problem which future research is expected to elucidate. It resolves to some phases of the effects of light on animal nutrition, a field which, to my knowledge, has not as yet been fully worked out. However, there seems to be a considerable evidence that air and sunlight help in the causation of the disease. Certainly they seem to partly protect the lower animals from acquiring it in their wild state and the natives in their own tropical homes. But, in exactly what manner their deficiency induces rickets, remains still to be shown experimentally and if possible, clinically. As a whole, defective hygiene in general may exert an influence in the development, or even may modify the course of the disease , but, to say that it is the most essential or primary factor, we do not feel at present provided with sufficient evidences. Furthermore, in some instances, its effects appear to be inconstant.[8]

6. Infection and Relation to Other Diseases.

The infectious causation of the disease (rickets) is also a debatable point. Moussu[49] and Koch[50] advocate rickets to be of the nature of infection and Morpurgo[51] claim to have produced true rickets in white rats by bacterial inoculation. The theory of infection as the cause of rickets is not as yet proved to warrant a definite statement. Moreover, rachitic and non-rachitic children may be housed together without the latter running the danger of contracting the disease.[32]

While we cannot say that microbic infection directly causes the development of rickets, still other infectious diseases may predispose or activate the morbid process. Lee[52], who made an investigation among three thousand cases, lays stress, as the precedent cause, on some form of pulmonary disturbances as bronchitis, broncho-pneumonia, and other lung affections. He considers that the imperfect or insufficient expansion of the lungs is the determinant of intercostal retrocession. This opinion, however, can hardly be made tenable, since it is equally plausible that the pulmonary manifestations may be secondary to the effects of the thoracic deformity[3]. Of course, it is not improbable that acute infectious processes during or preceding the onset of rickets, may aggravate the possible pre-existing rickety state, but certainly they do not directly cause the development of the lesions. On the other hand, chronic morbid processes as tuberculosis[1], or marasmus,

may not render the child vulnerable to the ravages of rickets. This is further shown by Baxter [44] who maintains that a marasmatic child ~~from starvation~~ by the protracted consumption of starch, may die of inanition, but the post mortem findings do not indicate traces of rachitic lesions. Furthermore, as shown by him, [44] it is possible that an infant suffering from prolonged ill health may be severely affected with syphilis but yet may escape rickets.

This brings us down to the consideration of the relation of rickets and syphilis. There has been a considerable dispute as to whether or not the two conditions are one and the same, and as to whether or not one predisposes the development of the other. Parrott's [53] denial of the existence of rickets as a separate disease and his arguments that the condition is but a phase of congenital syphilis, have aroused a considerable antagonism among the medical minds. Without going into a long discussion to show the views to the contraty, it is commonly admitted that the two processes are not clinically and pathologically identical. That they may exist in the same individual, has been however, regarded possible. In this connection, it is noteworthy that craniotabes, which as has been said before, may be seen in rickets, is, according to Lee and Barlow [11], chiefly caused by syphilis. They [11] entertain the view that a syphilitic child may

be as liable to the injuries from a faulty diet as a normal child. In other words, it is not impossible that rachitic changes may develop in a syphilitic infant; and if so, theexistence of craniotabes in syphilis as well as in rickets, may be partly explained. But whether or not, the craniotabetic patches are, in the two diseases,histologically identical,remains to be shown. However, it must not be construed that syphilis causes rickets; but that it may predispose or modify the rachitic manifestations, supports do not seem to be lacking.

7. Altered Function of Internal Secretion.

The disturbance of some of the endocrine glands has been regarded by some as responsible for the development of rickets. Thus, Matti,[54] Basch[55], Klose and Vogt[56], Stoelzner[57], and more recently Garrod[58] claim that the absence, extirpation, or possibly the affection of the thymus gland may produce rickets. It may be interesting to note, in this connection, that, in his investigation on the thymus gland of children, Dudgeon[34] found, in every case of lymphatic hyperplasia on the post-mortem table, well-marked changes in the bones resembling rickets. The results of experiments along this aspect of the subject have been rather inconstant[32] but it is impossible to disprove that there is no such altered function in the gland considering its important role in the general metabolism . But whether such alterations are primary or secondary to the disease-process,it is not yet known. Much is

still expected in the study of the physiology and pathology of the organs of internal secretion to elucidate some of the obscure problems connected with nutrition. However, it may not seem dangerous to state that a hypothetical abnormality involving the ductless glands is not antagonistic to the dietetic explanation of the disorder in question.[37]

(Next Sheet)

B. Determining Factor

Errors in Diet.

We have thus far discussed the factors that may predispose or contribute to the development of rickets. We pointed out that none of them seem to be the sole responsible agent in bringing the disease into existence. There remains for us to consider one more condition which may perhaps determine the onset of the morbid process......and that is, the "Errors in Diet".

1. The Rachitic Food and the Anti-Rachitic Factor.

In the earlier writings, we find that opinions were divided as to whether or not "dietetic error " is primary or secondary factor in the setting-in of the rachitic lesion. It should be recalled that Palm[16], Hirsch and Creighton[2], regard the lack of sunlight, the faulty ventilation, and the other defects of physical and hygienic conditions as more essential than improper food. On the other hand, metabolic error has been regarded by many as first in the list, which in conjunction with the effects of defective hygienic conditions , may, in large measure, determine the disease. But whether or not this nutritional disorder was due to improper food or defective assimilation, the older investigators were not able to say.

Although rickets may be considered as essentially a

disease of nutritional deficiency still we are by no means justified in regarding that the same foods, the consumption of which may lead to general metabolic disorder, are productive of the rickety condition. In other words, while the disease may in the protracted state, show signs of emaciation, still a marasmatic condition, due to starvation, as has been remarked above, may not welcome the coming-in of rickets. Moreover, it is not an exceptional experience that rachitic changes may develop in a healthy child of a well-to-do family and may go on in its process of development in a fat, apparently well-nourished infant. Therefore, it may be inferred that the rachitic process is a special nutritional disorder produced by one type of food in the same sense that scurvy is initiated by the scorbutic diet.

If we admit that the rachitic diet is mainly responsible for the disease, two things at least are implied: (1) By not giving it to a normal growing infant, rickets will not develop; (2) By removing it from a rachitic child, the rachitic process is arrested or improved. Can we conceive of an abnormal nutritional process caused by a diet otherwise abnormal ? If not, then we are admitting that the normal balanced diet must necessarily satisfy the two points mentioned above. Such being the case, and if we assume that

a = the normal diet
b = the rachitic diet,

what would be the result if b is subtracted from a? For the lack of a better word, the remainder is the so-called anti-rachitic factor. Now, the question is : What constitutes a rachitic diet and what is the nature of the anti-rachitic factor? It may be possible that by a knowledge of the components of the rachitic diet, the nature of the anti-rachitic factor may become apparently obvious, and vice versa. This may be so if we consider the anti-rachitic factor as a tangible substance; but, it may be an element, the presence of which, of course, may be assumed to be directly or indirectly concerned with the proper nutrition and physiological stability of the cells and tissues that are characteristically involved in the disease. This relation of the anti-rachitic factor with the body nutrition will be considered in more detail later.

1. a. Milk.

The rachitic food, then, is one destitute of the anti-rachitic factor. Is milk a rachitic diet?

Quite a number of investigators assert that premature weaning causes the development of rickets. The prevalence of the disease among the negro babies as observed by O'Donovan[45] in the Black District of Baltimore, has been regarded by him as due to improper feeding and early removal from the matennal milk supply. On the other hand, cases of rickets have been observed to develop

after prolonged suckling.[32] But, it seems to be a common finding that a breast-fed infant is less liable to be affected by rickets under similar conditions than a bottle-fed baby, although breast milk can not assure of protection nor cure the disease once developed. The nutritional value of human milk may be further shown that in some cases it may modify the course of the disease.[26] On the other hand, severe forms of rickets may develop in a breast-fed child if the nursing mother cannot give an adequate supply of the particular substances concerned with proper nutrition. It is said[37] that she obtains from the milk she drinks and from the eggs, butter, green vegetables and other food stuffs that she eats, these accessory food factors, which "are passed on to her mammary glands, thereby allowing the breast-fed child to get an adequate supply". It may be deduced therefrom, that unless otherwise proved abnormal, wet nursing should not be denied in preference to bottle-feeding. In other words, premature weaning may prove harmful to the metabolism of the infant, unless the food substituted is not devoid of the dietary"essentials."

The cow's milk has been regarded as productive of rickets.[1] It is undoubtedly inferior in quality to the normal human milk as far as the food essentials are concerned since the cow derives them solely from the green leaves of grass and plants. This may probably explain why rickets among children brought up on cow's milk developes more commonly in winter when the cows are no longer grazing on the green pasture lands. Similarly, Osler[9] says that the disease is common in children fed on condensed milk and other

various proprietary foods, while Howard[23] cites a case of a rapidly developing rickets in a child of ten months old, born from healthy parents, without hereditary tendencies, but fed partly on Swiss milk and partly on a patent farinaceous food.

Then, the next question, where is the fault of the preceding diets? Is it in the disproportion of the starch, mineral, protein and fat contents?

1. b. Starch.

The over consumption of starchy food has been considered harmful to the proper nutrition of the growing organism and responsible for the development of the rachitic process. Barlow and his co-worker[1] expressed the idea that potatoes and other starchy foods administered prematurely to poor infants, tend to produce irritating dyspepsia, and so indirectly to mal-nutrition and irregular bone development. Similarly, Holt[26] says that the excess of carbo-hydrate intake and the deficiency in fat content may lead to the development of the disease. It is possible that the consumption of exclusively starch dietary may produce a state of general mal-nutrition but not necessarily rickets. It should be recalled, what Baxter[44] remarked, that an infant fed on starch alone may die of starvation but the lesions are those of inanition and not of rickets. However, he gives no objection if it is conceived that starch may operate indirectly by interfering in some

way with the assimilation of fatty matter.

The supporting pillar, which the advocates of the "starch theory" of the causation of the disease hold, is founded on the presumption that the improper use of such a diet leads to gastro-intestinal disturbances. It should be recalled that symptoms of gastro-intestinal catarrh may precede the appearance of rachitic lesions. On the other hand, Findlay,[32] shows statistically that the symptoms of gastro-intestinal disorder before the onset of the disease are not soundly justified, and asserts that diarrhoeal manifestations in some cases are due to the state of malnutrition which is a frequent sequel of the disease.

Again, it may be assumed that, subsequent to the imperfect and fermentative digestion of the starch, lactic acid is absorbed into the blood which seems to exert an irritating action on the osteoplastic tissue[22], and set up the morbid changes similar to those of rickets. But Cheadle[7] says that the formation of lactic acid has not been confirmed and that rickets may develop without apparent gastro-intestinal disorder to favor lactic acid fermentation in children who digest starchy foods thoroughly.[7] Moreover, he observed that rachitic individuals became well while on farinaceous diet, by the addition of some other food constituents. And agai lean meat, which is not productive of lactic acid, may cause rickets when given exclusively to animals.

The "toxic theory" of the causation of the disease is offered by Marfan[59] who maintains that rickets is due to auto-intox-

ication from the gastro-intestinal tract.It may be of interest to recall that, according to Jacobi,[24] the"rachitic constipation" preceding the development of rickets favors the absorption of toxin from the fecal liquids. And Dudgeon[34], among the other causes which he mentions, offers the possibility of the absorption of toxin from the intestinal canal. As a whole, there are no sufficient evidences on this aspect of the subject to warrant a conclusive statement. However, it may mean a great deal of value if some works are to be done with regard to the possible toxic causation of the disease.

1.c. Mineral Content (Calcium).

As it is known that one of the characteristic lesions of the rachitic bone is the diminished content of calcium, it may seem at first probable to assume that rickets may be produced by the lack of calcium salts in the diet. If that be so, how would one account for the development of rickets in limestone districts where there is invariably an abundant supply of calcium salt by the use of the lime water in their food? Likewise cow's milk is richer in calcium salts than human milk, and yet the former is more provocative to rickety development.[1] And although experimentally, bone changes may be produced by the persistent administration of diet poor in calcium, still the histological examination shows that they are not true rickets[26] but an osteoporosis

Moreover, the therapeutic administration of calcium salts to rachitic patients does not lead to a cure; on the other hand, a spontaneous improvement may appear without treatment and without alteration in the food.[1]

1.d. Protein and Fat.

Lastly, we come to a consideration of whether or not a disproportion of the protein and fat content of the food plays a part in the formation of the rachitic diet. Cheadle[7] seems to answer this question by asserting that a diet in order to be rachitic, must have a decidedly insufficient supply of animal fat, with more or less deficient amount of calcium phosphate, and probably an alteration in the protein content.[7] He points out that fat is probably essential to all cell-life and growth, lime phosphate to every tissue especially to the bones, and protein to the vitality of the protoplasm . He argues that if the protein is in excess and the other elements deficient, the progress of rickets may be intensified by the stimulation of the process of tissue development, which, in the deficiency of the other materials, is apparently deviated in its normal direction(in the building of permanent structures.) On the other hand, if the protein content is deficient, the corresponding insufficient supply of animal fat and calcium phosphate may determine the onset of the disease, and may explain for the lesions in the bones, the feebleness of the muscles, the nervous manifestations, the weakened constitutional

vitality, etc. Findlay,[32] however, entertains the idea that deficiency of fat in the diet is unlikely the cause of the disease, and cites instances in which a child developed rickets while on a diet rich in fat. However, his evidences do not seem to be conclusive, and the case in question might have been incidental; in other words, some other process or factors might have been at work or that the fats used might have been drained from the digestive tract[7], due to some possible diarrh~~o~~ea, before they were digested and utilized by the tissues..

The type of diet, such as Cheadle[7] describes, poor especially in its fat content may account partly, if not chiefly, for the development of the bone deformities diagnosed as rachitic among the young animals in the zoological gardens. It should be recalled that by resuming the milk or by adding cod liver oil in the diet, Bland-Sutton[35] experienced that the deformities were not only prevented and arrested in their development, but also improved so that the young animals could grow strong and apparently healthy up to their full size. It may be deduced, therefore, that there is somethig in the cod liver oil and milk which supply what was lacking in the former diet of the animals; and that this is the still-unknown "food-accessory" anti-rachitic factor.

2. Specific Causation and Pathogenesis.

Now, it remains for us to consider the specific causation and incidentally the possible pathogenesis of the disease. We know that rickets is characterized mainly by the defect in the ossification of the bones , and that the process of ossification is apparently in relation to the calcium metabolism. Therefore, it may be implied that the explanation of the rachitic process does not seem to be very far from this point.

2.a. Calcium Metabolism.

It has been fairly established under the Chemistry of the Bones, that the proportion of calcium content of the rachitic bone is far less than that of the normal. And we have also shown above in the discussion of what constitutes a rachitic diet that, a deficiency in the calcium content of the food alone does not lead to the development of the disease ; on the other hand rickets has been found to occur in the abundance of calcium supply and phosphoric acid[22] and that cases of spontaneous recovery have been recorded without any change in the diet intake and without therapeutic assistance[1] ; and that even if associated with insufficient calcium supply, the cure of the disease by the administration ofthe salt is not always assured. Moreover,although a rachitic-like condition of the bones may be produced experimentally still it was found that histologically there were no osteoid

tissue and that the changes were osteoporosis rather than true rickets where, unlike human rickets,[20] the soft tissues share in the calcium deficiency, and the lesions disappear by calcium administration. Now then, where does the fault lie? Is it in the form of decalcification of the bones already-formed ; or, if the calcium supply is abundant, is the fault in the rapid elimination of the salt from the intestinal tract without first being absorbed into the blood stream, or is it in the defective fixation of the calcium by the growing bone tissue?

The idea of the decalcification of a fully formed bone in rickets has not been lacking advocates. The former supporters of the acid theory in the causation of the disease have conceived the existence of lactic acid in the circulation subsequent to the fermentative digestion, which dissolves the lime and prevents it from being deposited in the bone. Heitzmann[60] , who claims that rickets can be produced by the persistent inhalation of phosphorus or lactic acid or by subcutaneous administration of the latter to an experimental animal, believes that the acid thus formed and existing in the circulating blood irritates the osteoplastic tissue leading to perverted growth.However, even if we assume that there may be an irritating substance in the blood,such can hardly be regarded in the nature of lactic acid since, as has been above stated, rickets may develop in children without history of gastro-intestinal disturbances to account for the formation of

lactic acid, since rachitic manifestations may disappear even when the starchy foods are continued, and since rickets may develop by the use of lean meat alone which does not yield an appreciable amount of lactic acid. Cheadle[7], Stoelzner[20], and others assert that lactic acid has not yet been demonstrated to accumulate in exdess in the rachitic blood, nor has it been found in the urine of a rachitic individual.[7] Moreover, diabetes does not seem to predispose the development of rickets and that the administration of sodium-bicarbonate is not clinically proved of therapeutic value in the latter disease.

However, although lactic acid is not proved to exist in the rickety infant, still we are not fully justified in assuming that there are no irritating substance or substances in the circulation. Barlow and Bury[1] claim that the irritating substance is derived from, among other sources, the "altered nutrient juices", which exerts its action on the delicate ossifying tissues. The hypothesis is supported by Cheadle[7] and Jacobi[27] who maintain that the excess of the irritating agent is responsible for the increased vascularity of the bone-forming tissues, and the proliferation of the cells in the growing portion of the bone. This phenomenon suggests a chronic inflammatory process which Kassowitz[61] regards as the beginning of the disease. He[61] induced hyperaemia by the application of Esmarch's bandage on the limb of a growing animal and showed that the increased blood flow had not only prevented

the deposition of lime but also caused the melting away of the fully-formed bone. But while, by this process, a ricket-like condition may be observed in the bones, still we are, by no means, warranted in asserting that the other tissues are likewise affected and present changes such as are found in the rachitic subject. Furthermore, it may be presumed that the increased vascularization and the subsequent enlargement of the blood vessels cause, according to Cheadle[7], a pressure upon the septa between the medullary spaces leading to a partial absorption of the old bone and subsequently a deficient ossification of the new bone. And he[7] believes that this accounts for the brittleness and softness of the rachitic bones. However, one would not feel satisfied if the pathogenesis of the calcium deficiency of the rachitic bone is only explained by the erosion of the bone due to pressure of the proliferating blood vessels unless the rachitic osseous changes can be made comparable to those produced by aneurisms and other vascular alterations pressing upon the bone. Moreover, while Barlow and Bury[1] implicitly entertain the view that it is not yet determined what place rickets holds in the many connecting anatomical links between a simple hyper-plasia and an inflammation, still they frankly express :

> "The plain and practical outcome of a study of these changes is, surely, that we have to deal with an irritative overgrowth of the osteogenic tissue, and that this and not the deprivation of lime, is the primary fact in the disease."

Some aspects of the decalcification process, therefore, are still debatable. If it may be demonstrated that there is an excess of calcium output over the intake, the presumption is that some of the excreted calcium might have been partly abstracted from the tissues. But, whether or not, this is exclusively extracted from the already formed bones or from other sources, is still a subject waiting for farther investigation. However, it may be of interest to note, in this connection, that according to Stoelzner[20] the soft tissues of rachitic children contain no less calcium than normal.

Now, we are in the second part of the former question, namely: If the calcium supply is abundant, is the faulty ossification due to the rapid elimination of the salt before it is absorbed into the blood or to the defective capacity of the osteogenic cells to utilize it?

While admitting that in rickets, there may be a diarrhoea which drains the calcium supply as soon as it is ingested, yet the assumption that, in the absence of gastro-intestinal trouble, the retention of calcium salts is not diminished in the rachitic infant seems to be unwarranted. Findlay[3], from the statistical data that he quoted from various authors, seems to point out that the calcium retention in rickets is below that of the normal, and in some instances, the output may even be more than the intake.[3] He also regards age, exercise, and diet as im-

portant factors that may influence the retention.

The role of fat in the calcium retention is still controversial.[3] However, it is said that, while other fats may cause a fall in the amount of calcium retained, still cod liver oil and Sesame oil were found to apparently increase the retention. The therapeutic value of the cod liver oil as has already been discussed, may be therefore, justified. On the other hand, Vierordt[62] believes that the lime absorption during the development of rickets is as good as in normal. Moreover, in the studies of Findlay[3], the variations of the output were great in periods of a few days that he deems necessary to repeat the investigation after establishing a calcium equilibrium, before anything definite can be made with regard to the retention of calcium salts.

The retention question, however, would be of little moment, if we disregard that the excreted calcium through the feces (and not through the urine[34, 47])may be partly from the unutilized salt due to the defective power of the bone-forming tissue to fix it. In other words, a certain stage of the morbid process, will be reached when the decalcified remains of the new-formed bone, even with an abundant supply of calcium brought to the cells,are no longer capable of absorbing it.[20] This explains the persistence of the disease when calcium alone is given therapeutically.

The failure of the epiphyseal cartilage to fix the calcium seems to be an interesting question. Wells[63] introduced into the peritoneal cavity of a rabbit costal epiphyseal and tracheal car-

tilages[63]. He observed that all the tissues absorbed calcium but the epiphyseal cartilage absorbed only as much as if it had developed into bone. However, whether or not normal and rachitic cartilages exhibit different fixing power to calcium, is still a problem.

On the whole, the metabolism of calcium is not yet clearly understood. There are many open queries and unsatisfied. The role of the organs of internal secretion, which seems to be of considerable importance in this aspect, has not yet been much dwelt upon. However, in this connection, Findlay,[32] states that calcium metabolism in rickets and thymusectomy, exhibits certain differences. Thus, while in rickets the chief route of the excretion of the lime is by way of the feces, in thymusectomy the calcium is mainly excreted, just as in starvation and diabetes, by the urine. The analysis of the blood and of the soft tissues, as far as the calcium content is concerned, presents so wide a variation both in rachitic and non-rachitic individuals, that further reliable data seems to be indispensable before anyone feels safe in emitting a sound judgment. This is, of course, of considerable importance in order to answer the question : Where does the organism derive its calcium supply in the building up of bones if the intake is insufficient?

The study of the influence of other dietaries such as starch, protein, etc., besides fat in varying proportion, has been apparently neglected, for no available information is ob-

tainable . However, the effect of certain "accessory factors" in the deposition of lime has created recently a considerable interest which, in the belief of modern investigators, seems to be pointing to a narrower field for the search of the specific causation of the disease. In other words, the so-called "anti-rachitic factor" is presumed to be one type of food accessory essential found in the cod liver oil, in animal fat, and in various other sources; the absence of which is regarded to be mainly responsible for the rachitic process, and the influence of which, on the proper calcification of the growing bone, may, by way of animal experimentation, be observed even roughly quantitatively to be comparable to the lesions at the corresponding stage of the disease in man.

2. b. Animal Experimentation.

Our discussion has brought us to a consideration of the possible specific agent that leads to the development of the disorder. We now come to admit that there is such a thing as a "rachitic diet " and an "anti-rachitic factor" . We also showed that the lesions are not caused directly by digestive disturbances due to improper and untimely ingestion of starchy foods alone, nor by the lack of calcium salts in the diet, although, however, Cheadle[7] indicated that the lack of animal fat and, to some extent,

of protein is an important etiological factor.

We also have come to a consideration that, as rickets is most constantly manifested by changes in the bones, the root of the disorder is probably somewhere in the faulty metabolism of calcium. Although calcium in the form of phosphate is essential to the nutrition of the tissues, the lack of it in the food does not necessarily induce the development of rickets, as has been shown experimentally.[20] Likewise, the abundance of calcium supply does not always immunize or insure a protection against its development. In other words, the proper metabolism of calcium salts does not lie in the quantity of the salt ingested, for it has been found clinically that rickety manifestations disappeared spontaneously in diet whether deficient or abundant in its calcium content. However, that the proper utilization of the calcium brought to the osteogenic cells may be influenced by other factors or constituents in the food, is commonly admitted by modern experimentalists. The truth of this statement may be supported by the justified therapeutic administration and the beneficial effect of cod liver oil, milk and its by-products, animal fat, etc. and not calcium alone. Now the question arises: What specific substance or substances in the cod liver oil prevent, arrest, and cure rickets?

Numerous experiments have been made and are still being conducted along this line of work. While there can be no

doubt that the starch, protein, fat, and mineral salts in the diet are essential for physiological existence, still it cannot be denied that there are accessory factors in the food which are equally essential to nutrition, physiological stability, and perhaps growth. Osborne and Mendel[64], in their experiments on "Protein-free" milk, found that growth could be maintained for a time, the cessation of which could be prevented by the addition of butter. In a later publication, they[65] showed that this "essential" accessory growth-promoting material exists in butter-fat, egg yolk-fat, and other substances. Our knowledge of these growth-promoting substances has been rather meagre until McCollum and Davis[66] in their series of animal experiments, identified the unknown, accessory, essential dietary factor by saying:

> "The experiments already described force us to accept the conclusion that *there are necessary for normal nutrition during growth two classes of unknown accessory substances, one soluble in fats and accompanying these in the process of isolation of fats from certain food-stuffs, and the other soluble in water, but apparently not fats.*"

In a later publication, they[67] confirmed these views, which gave birth to the terms "fat-soluble A" and "water-soluble B"[68]. Without going into a long discussion of the so-called vitamines, there are, up to the present, found three food accessory essentials[6 viz:

> "1. Anti-neuritic or anti-beriberi factor, identified with Water-Soluble B factor of the American investigators."

2. "Fat-soluble A growth factor or anti-rachitic factor.
3. Anti-scorbutic factor."

And the report of the Committee[69] continues:

> "As far as is known the accessory food factors cannot be produced by the animal organism, and all animals are dependent for their supply directly or indirectly upon the plant kingdom."

Obviously, we are here solely concerned with the fat-soluble A factor. But the question is: Is it or is it not the anti-rachitic factor ?

The fat-soluble A is a food accessory essential concerned with the growth and maintenance of normal existence. Its true chemical nature is yet unknown. According to McCollum, Simmonds and Pitz[70], it is found in the butter-fat, egg-yolk, maize-kernel, wheat embryo, oat-kernel, leaves, etc. from which sources, the nursing mother may derive enough supplies for her milk since she cannot systhesize it[71].

The essential accessory factor (fat-soluble A) is so important as a food constituent that its absence has been regarded as the cause of some pathological condition in experimental animals. Thus, xerophthalmia has been found associated with the lack of this supply.[36] May Mellanby[18] succeeded in demonstrating the various grades of dental development among her experimental growing puppies by subjecting them to a diet with different amounts of this unknown factor. She entertains the view, by the lack

of this accessory essential in the blood, the ameloblasts are weakened in their regulating function to deposit the calcium salts although in abundance in the developing teeth. She found that the decrease in the enamel content of the teeth was more or less in relation with the lack of fat-soluble vitamine and that the dental morbid process was worse in the more rapidly growing animal. She also correlates these findings in the experimental animals with the carious condition of the teeth not uncommonly associated with the development of rickets in the growing infant. And then in her conclusion, she says:

> "This work taken in conjunction with the experiments of E.Mellanby on rickets, puts the close relationship between hypoplastic teeth and rickets on to an experimental basis."

The results of Edward Mellanby's investigations as published in the Special Report No.38 of the Medical Research Committee[37] semm to indicate that the fat-soluble A is identical with the anti-rachitic factor. He[19] conducted the experiments on 200 puppies, subjecting them to different diets known to produce rickets and subsequently adding to the standard diets other substance to determine the effect of these in the development of the disease. Without going into detail in the description of his experiments, the substances that he found to prevent rickets may be grouped into two categories: (1) that of extractives, and (2) that of fats. He observed that the animal fats were more

effective in preventing the disease than the vegetable fats. He draws the relation between the fat-soluble A and the anti-rachitic factor by saying :

> "It is known, for instance, that animal fats are a good source of the fat-soluble A factor and that vegetable fats are deficient. Similarly, the anti-rachitic factor is more abundant in the animal fats than in the vegetable fats."

And then he continues:

> "....rickets is a disease accompanying growth and it appears that the more rapid the animal grows, the more anti-rachitic factor is necessary to keep the growth normal. Since,however, it is recognized that both fat-soluble A and water-solubleB are necessary for growth per se, in so far at least as rat-feeding experiments are concerned, it might, at first sight, seem strange that a disease of growth should have its explanation in a deficiency of a growth accessory factor."

And, in his conclusion, he states:

> "The anti-rachitic factor has, in many respects, a similar distribution to the fat-soluble A factor and is possibly identical with this substance."

This last view, however, does not seem to agree with the observations of clinicians and other experimentalists. It can hardly be accepted as feasible in the sense that Hess and Unger[8] observed infants developing rickets when fed on a diet rich in fat-soluble vitamine; on the other hand, they[8] observed infants not manifesting any rachitic sign while on a diet devoid of this factor for many months. Moreover, the infants, according to them, could maintain their health and vigour despite of the minimum

amount of the fat-soluble A factor ingested.

Similarly, McCollum, Shipley, Park, and co-workers[36] carried out extensive experiments on 2,000 rats with a view to find out the nature of the specific causative factor of the disease. The problem was attacked from two angles: (1) the development of rickets in animals fed on certain ration, and (2) the improvement of the lesions after cod liver oil administration. Without going into detailed account of their experiments, the gross lesions of rickets could be induced by diets containing varying proportions of calcium, fat-soluble A (butter-fat), and other dietaries and were found to have no direct relation to the quantity of fat-soluble vitamine present. In other words, an abundant supply of fat-soluble accessory in the diet with low calcium content did not prevent the development of the gross rickety lesions. On the other hand, by using the same type of diet, but supplemented with a certain amount of cod liver oil, rickety changes could not only be prevented but also became improved, shown by the deposition of a fine line of calcium phosphate in the cartilage. The probability, therefore, is that the cod liver oil furnished the anti-rachitic factor without which rickets developed even if the diet had contained abundant fat-soluble A essential. In other words, the anti-rachitic factor may be presumed to be distinct from the fat-soluble accessory.

There remains, however, a question to be settled.

In the event that xerophthalmia and decayed teeth are produced with lesions of rickets, the administration of an anti-rachitic factor may be conceived or expected to improve the rickety state alone without altering the eye and teeth lesion. On the other hand, if a diet is so constituted so as to improve xerophthalmia and dental hypoplasia without affecting the rachitic manifestations, then such a diet may be presumed to be devoid of an anti-rachitic factor. Furthermore, if the anti-rachitic factor alone can not be made to cause a defective dentition, then we may assume that we are dealing with a specific factor mainly for the nutrition of the osteogenic and other tissues concerned in rickets. Much is therefore expected in this line of study.

The beneficial effect of the cod liver oil on the ossification of the bones which have been previously rendered calcium-free, was shown by them[36] to be comparable to the process of repair of the human rachitic bone in the period of convalescence Their experiments were checked by control animals, and the bones of both groups were subsequently examined under the microscope. They found that the addition of cod liver oil to the food of the rachitic animals was followed by the deposition of calcium salts between the cells of the proliferative zone. It seems possible, therefore, that the cod liver oil besides lessening the harmful effects of too much or too little lime, may increase the capacity of the osteogenic tissue to absorb or fix the calcium salts brought to them. This calcium-depositing potentiality of the

cod liver oil could also be manifested even if the lime intake was far below normal, and it is a question where the animal under such circumstances, derived its calcium supply for the building of osseous structure under the influence of the oil.

From the above considerations, we may deduce that there may be another unidentified,food-accessory essential, or an unknown X associated with the cod liver oil, which is probably different from the fat-soluble A , although, in the opinion of McCollum[72] , it may likewise be found in butter-fat, egg-yolk glandular organs, degerminated seeds, leaves of plants, animal fat, but not in vegetable oil. It is possible that the absence or deficiency of the hypothetical agent in the food may presumably decrease the capacity or weaken the function of the bone-forming tissues to utilize the calcium salts. This view,may not be held untenable, since the anti-rachitic factor in the cod liver oil is assumed to be concerned with the increased deposition of the calcium salts in the active or growing portions of the bones. In other words, the persistent consumption of a deficient quantity of the sources of the undetermined factor or the habitual intake of an excess of foodstuffs containing less of it, may operate in diminishing the nutritional state of the growing cells, and in conjunction with other yet unknown mechanism, may pervert growth and lead to the development of rickets.

2. b. Present State of the Problem.

On the whole, despite the large amount of work done, our knowledge concerning the disease is still deficient. Many problems on the pathology of rickets, as have been above indicated, are still untouched or at least unsolved. In this connection, the statement of Noel Paton and Findlay[73] is noteworthy, namely:

> "Further research on the chemical and histological changes of the various tissues, e.g., the muscles and of the metabolism of calcium is required."

It should be here emphasized that the thorough knowledge on the calcium metabolism and the role played by the organs of internal secretion in normal and diseased processes of nutrition and growth, will not be undoubtedly of unesteemable value in the elucidation of the pathogenesis of the disease.

The etiology of the disorder is, likewise obscure. The predisposing factors, as above described, may each have a share to prepare the field in the delicate, growing, human body, for the specific agent or condition to operate. The real cause is not yet definitely known. The suggestion of McCollum, Shipley, Park, and others[36] that the lack of an unidentified food accessory (the unknown X) in the cod liver oil, essential for nutrition of the growing cells and distinct from fat-soluble A, is partly if not mainly the cause of the disease, seems to be plausible and supported by experimental evidences. However, the "irritation theory",

proposed by Cheadle[7] Barlow and Bury[1],and others, —the irritant being derived from the altered condition of the unbalanced food in the blood— by which the proliferative changes of the blood vessels and the increased amount of cartilage cells in the growing portion of the bones may be explained, cannot be entirely ruled out. On the other hand, it may be made to support the former view.

The part played by the unknown X in modifying the rachitic lesions is therefore an interesting subject for speculation .It is conceivable that the anti-rachitic factor is concerned with the functional activity of the growing cells; but whether or not it exerts its action directly upon the cells or indirectly upon other metabolic products harmful to the cells, is, as far as I am aware, not yet determined.While it is possible that the unknown X per se may be nutritive to the growing cells, still it cannot be regarded as impossible that, by taking part in the proper metabolism of the other food constituents, the subsequent formation of substance or substances in the blood detrimental to the growing tissues, may be prevented.

Aside from this hypothetical preventive action, may we not be also justified in assuming that the unknown X exerts an inhibitory influence or a neutralizing effect on any metabolic product, harmful to the osteoplastic tissue? And, if assuming that such altered metabolic irritating substances are formed in the absence or deficiency of the unknown factor X and that by their

action on the growing portion of the bones deficient ossification results, would it be erroneous to suppose that the unknown food accessory factor supplies the energy to the cells so that an impetus is always brought about for the completion of the building of permanent structures ? The acceptance of the latter hypothesis does not, however, seem to be antagonistic to the view expressed by McCollum, Shipley, Park, and their co-workers[36] that the cod liver oil regulates the deposition of the calcium salts by modifying the capacity of the osteogenic cells to fix the salts brought to them. In other words, the lack in the food of the accessory dietary essential (the unknown X), such as abundantly found in cod liver oil, would obviously inhibit the functional activity of the osteogenic cells to utilize the calcium properly to ossify the cartilagenous structures, which are found to be apparently proliferating through the stimulating effect of the abnormally metabolized products. Whether or not such or similar hypothetical explanation may be applied to the changes in the soft tissues not infrequently involved in the disease-process, is still a question for further study.

There is one more point before closing. While Shipley, Park, McCollum and their co-workers[36] demonstrated convincingly the deposition of calcium following the administration of the cod liver oil at the epiphysis of the rat bones comparable to the process of repair of the human during convalescence, still as far as

I can make it out, the osteogenesis beneath the periosteum has not been mentioned. May we not be justified also in assuming that the unknown X nourishes or activates the periosteal osteoblasts as well as the cells in the "growing zone"? If so, is the resulting calcification comparable to the "eburnation"[22] of the human rachitic bone during its period of re-construction? In other words, were the bones of the experimental rats stronger than those of the normal after recovery from the disease ?

If the unknown X starts the lime fixation after the bones have been previously rendered calcium-free by diet, we would expect that the absorption continues as long as the factor is given. But, is it impossible to demonstrate whether or not this impetus may be arrested by stopping the oil administration ? In other words, by withdrawing the therapeutic agent little by little, will the experimental animals show, as far as calcification is concerned, changes pointing to a reversed process ? Do we have evidences at hand to minimize the possibility of other factors or conditions that may continue the process of ossification, once started, even if the unknown essential is then withdrawn? Is there such a thing as immunity or tolerance in rickets ? And in addition to this, will the serum of a rickety individual, after having been administered sub-cutaneously, to susceptible animals (as rats) cause, predispose, or prevent the development of rickets when the diet destitute of the unknown X is given?

The foregoing "addenda" are, in my opinion, other fields of action in the way of animal experimentation, if the latter is hoped to point to a nearer solution of the problem at issue.

IV. Summary and Conclusions.

1. Rickets is a chronic constitutional disease of early childhood caused by a deficiency of nutrition, and manifested by abnormal changes in the muscles, ligaments, mucous membrane, visceral organs; indeed, of almost all structures of the body; but particularly of the bones which, subsequent to their faulty ossification, undergo improper development (as for instance, of their growing portions), and later on, various deformities with or without simple fractures at their shafts.

2. There are evidences to show that the disease existed in ancient times, and increased in frequency hand in hand with the progress of civilization. It was not however until about the middle of the seventeenth century, when Glisson first recognized it and classified it, in his famous treatise "De Rachitide" published in London in 1650, as a distinct clinical entity. He proposed the name "Rachitis" in preference to Rickets, which latter term, derived from the old English word "Wrikken" meaning "to twist", was then in popular use for the malady. The tfaditional name, "Morbus Anglicus" or "English Disease" which is somtimes used as a synonym of rickets, was given by the older writers that followed Glisson because, at that time, the disease was remarkably prevalent in England. Numerous investigators were aroused with interest in the study of the Disease, especially in its etiological aspect, but although several theories have been proposed, yet practically nothing definite was advanced until more recently, when in the studies of the vitamines, the"food deficiency theory"

has been unfolding gradually the hidden mystery of its causation and pathogenesis.

3. The diagnosis of rickets cannot safely be made without a thorough and combined knowledge ~~and~~ of its symptoms and physical ~~science~~ signs in the living, and its pathological picture at the post-mortem table and under the microscope.

4. The disease develops insidiously and takes a chronic course. Some of the early constitutional symptoms are : hyperirritability, restlessness, ill temper, inability to sleep, general pallor, muscular flabbiness or disinclination to support himself, and nocturnal perspiration especially in the region of the head and neck.

5. The physical signs may be summarized as follows:

(1) the head looks square--hence, "caput quadratum" --due to the presence of abnormal prominences over the parietal and frontal regions; the head therefore, appears larger than normal. The margins of the cranial bones are thickened, and the sutures and fontanelles widely patent. There may be thinned or parchment-like areas (craniotabes) over the parietal and occipital regions which yield on pressure. Dentition is usually delayed; and if the teeth have already appeared, they are subject to decay.

(2) the chest presents deformities and contractions to assume the so-called "pigeon- or violin-shape" alluded to by many as characteristic of the disease. The "rachitic rosary" in the costo-chondral

junction of the ribs, which may be more pronounced in the lower ones, has been found almost invariably to be associated with the disease. Beadings may also be found alongthe posterior axillary line of each side. In front of each of the rows of the anterior rosary beads, there is usually a groove placed obliquely on the chest wall. Similar depression may be seen transversely across the lower portion of the chest from the xyphoid process to the posterior axillary line on each side at about the level of the diaphragm; --this is the so-called "Harrison's groove".

(3) The abdomen bulges, due to the laxity of its anterior wall, to the increased abdominal pressure, and probably to the deformity (shortening) of the spine.The increase of the intra-abdominal pressure may be either due to the distension of the bowels or to the displacement of other visceral organs which may have been pushed downward by the contraction of the chest and possibly of the diaphragm, or both. There may be either diarrhoea or constipation subsequent to either disturbance of digestion or lack of tonus of the gastro-intestinal wall respectively.The pelvis may be so contracted and deformed that child-bearing may become a problem for the female victim when she reaches the conjugal age.

(4). The extremities present abnormal curvatures and enlargements over the region between the epiphysis and the diaphysis of the long bones. Such enlargements are usually more noticeable about the region of the ankle and wrist joints.

(5). Whether or not the rickety infant is emaciated or fat,is of

little diagnostic value; and, whether or not he is superior in intellect than the average normal baby, is not clinically proven.

(6) The muscles and ligaments are flabby and lax, and the child is apparently too weak to sit up or walk.

6. Due to the liability of a rickety infant to catarrhal diseases of the mucous membrane, and perhaps due to the mechanical pressure exerted by the contracted chest, there may be symptoms of bronchitis, broncho-pneumonia, collapse of the lungs, and other pulmonary affections. Associated with rickets, such nervous manifestations, besides hyperirritability and restlessness, as laryngismus stridulus, spasms of the glottis, tetany, or general convulsion, may also be found.

7. Whether or not anaemia is not invariable in rickets, is still a controversial question.The evidences on both sides are so balanced that no definite conclusions can be drawn. The blood picture in rickets, therefore, requires further investigation

8. The bone lesions are the most constant and characteristic features of the disease. The gross changes consist of : deformities and abnormal curvatures of the bones.

(1) The "cranial bosses" ahd the thickenings of the skull bones have been regarded as mainly due to vascular hyperplasia, while the craniotabetic patches as examples of atrophic changes. The teeth lack the enamel coating or the resistant material, so that they become remarkably brittle.

(2) The bones of the face and of the spinal column also suffer certain deformities. Due to the deformities of the pelvic bones, the pelvic outlet may become so contracted, that a history of rickets in a female individual may be of considerable importance from an obstetrical viewpoint.

(3) The abnormal bending of the long bones of both the chest (ribs) and of the extremities have been referred to as more or less associated with the disease. There may ~~be also~~ occasionally be simple "greenstick" fracture in the radius, ulna, ribs, humerus, femur, fibula, or clavicle.

9. The vascular hyperplasia of the germinal layer of the periosteum has been regarded as being responsible partly for the imperfect ossification of the shaft of the bones. Thus, the proportion of the inorganic (calcium especially) to the organic contents of the rachitic bone is much lower than that of the normal. But, while there may be a state of deficient calcification during the rachitic process, yet an "eburnation" may be observed during the period of reconstruction of the bone;[22] so that, after recovery, the rachitic bones may become firmer, more compact, and stronger than normal, although the microscopical elements of normal bone may be found to exist therein.

10. The enlargement of the "growing zone" between the epiphysis and the diaphysis of the long bones is the most characteristic lesion in rickets. In the normal, it is seen as a narrow, straight, glistening bluish-white line sharply demarcating the epiphysis from the

diaphysis. Under the microscopic such normal epiphyseal line may be seen to consist of regular parallel rows of cartilage cells along the axis of the bone, which later become confluent, enlarged and form the primary ~~bone~~ marrow spaces. The cartilagenous matrix becomes rapidly ossified so that the "osteoid tissue", if present at all, would be represented under the microscope as a narrow, insignificant structure. In rickets, this "growing zone" is markedly enlarged or thickened (occasionally 5 times the normal size)[26], and appears as a bluish cartilagenous mass with tongue-like irregular processes projecting into the diaphysis; in other words, the normal contour of the epiphyseal line is broken.

Microscopically, in this widened transitional "proliferating zone" or "metaphysis", there may be seen irregular islands of groups of cartilage cells, and large amount of unossified bony trabeculae. These are the "osteoid tissues" the abundant formation of which characterizes, in great measure, the rachitic process and the presence of which forms the most significant basis in the establishment of the diagnosis. Besides the osteoid tissue, there may be seen enormous quantity of connective tissue and apparently proliferating blood vessels which appear to be traversing the zone in all directions and at different levels, thereby destroying the striated appearance of the normal epiphyseal line.

11. The abnormal vascularization of the growing zone and of the inner germinating layer of the periosteum together with the apparent

hyperplasia of the cellular elements of the osteogenic tissue suggest an inflammatory process.

12. The soft tissues also take part in the disease process. The flabbiness and laxity of the muscles and ligaments have already been referred to. But, whether or not the muscular weakness is due to an actual atrophy of the fibres, or to functional disturbance, or both, we are not yet prepared to say. The subject is still waiting for further evidences.

13. The visceral organs show some pathological alterations. The lungs have been found, as above stated, diseased, probably as a result of the diminished function and subsequently the lessened resistant capacity due to the chest contraction. The occasional enlargement of the right heart in rickets, may, as in beri-beri, be possibly brought about by the resistance offered by the pulmonary circulation subsequent to the diminished respiratory field. The liver and the spleen have been considered by some to invariably take part in the process of the disease, but the anatomical lesions in both present so wide a variation among the rachitic victims and have also been found in other diseases, that a definite statement of an invariable enlargement of these organs in rickets, may be rather reserved until further research is made along this line. The gastro-intestinal tract presents no anatomical alteration outside of simple atrophy of the muscular coat as determined by Jacobi[24].

The possible pathological lesions of the brain and spinal cord need further investigation as the literatures are very meagre on the subject. Similarly, the pathology of the organs of internal secretion, is, as far as I know, still a virgin field. It is possible that there may be some distinctive yet unknown morphological alterations in such organs as thymus and adrenals, besides the supposed disturbance of their function.

14. The similarity of animal and human rickets has been clearly established based on the similarity of the etiological and pathological aspects of the disease as well as the similarity of their reaction to therapeutic agents. Although we may not be permitted to assume that"experimental"and human rickets are one and the same disease, still we may safely say that the"experimental rickets" is homologous to the human type as "polyneuritis gallinarum" to human beri-beri.

15. Although the disease has been first recognized in England, where it was, at that time, prevalent, subsequent investigations revealed that it existed in all quarters of the globe. It is more abundantly distributed in the regions within the temperate zone. It should be recalled that, according to Hirsch and Creighton[2]:

> "Its principal seats are: Germany, England, Poland, Belgium,France and Northern Italy; while southern provinces of Spain and still more,Turkey and Greece enjoy a notable immunity from it."

In the United States, it is not as abundantly scattered as in the European countries; it is apparently limited in large cities as New York, Philadelphia and Baltimore. The disease is rare in North Greenland, Faroe Island, Iceland, Norway and Denmark, --also less common in Syria, Arabia, India, Java, Cochin-China, Japan, Madagascar, Myotte and other Pacific Islands, Egypt, Algeria, Senegambia, California, west coast of Mexico, the West Indies, Guiana, ~~the West Ind~~ Buenos Aires, and Paraguay. Climatic conditions such as regarding altitude, temperature, sunlight, and humidity may influence its occurrence in the above regions; but, generally speaking the disease is rarer in tropical and sub-tropical countries and at higher altitudes "especially if the soil is dry"[1]; in other words, the disease becomes more severe in cold and wet climate and in wet places especially where the weather changes frequently such as found in those countries ~~above mentioned~~ where rickets has been reported ~~found~~ prevalent.

16. The disease has been found more frequent in the densely populated manufacturing cities of Prague, London, Liverpool, Glasgow, Vienna and New York City; in hospitals, asylums, and other allied infant institutions. Rickets seems to be more severe in cold winter than in summer months.

17. Although the disease may manifest itself clinically from childbirth until the age of puberty, the most dangerous age for children when they are most predisposed to the development of the disease, is from six months to two years. It is questionable whether or not fetal rickets exist clinically. However, cases of late rickets (as ~~far~~ late as the age of puberty) are on record, but whether these are recrudescence of an old existing mild lesion or not, no one can say.

18. The disease affects both male and female children equally. The prevalence of rickets among the negroes and Italians having the same food as that of other races, has been regarded by Holt[26] as due to racial peculiarities. However, the possibility of other factors outside of racial predisposition to explain its undue prevalence in these cases, cannot easily be ruled out.

19. Heredity per se as a factor in the causation of the disease can hardly be regarded as being sound, since we do not have evidences to show that rickets may be transmitted from the parents to the offspring through their primary genetic cells--spermatozoa or ovum, or both. But although this hereditary transmission may not be held as feasible, the hereditary predisposition, as above described, may become the dumping place of some, still

unknown, aspects of the disease. In other words, individual predisposition, acquired by the infant, may be considered as one of the contributory factors that prepare the field, in the body of the child, more productive or fertile for rickety development. The social and economic status, as well as the health, habits, and occupation of both parents, are factors that have to be considered in evaluating the parental influence in the predisposition of children under their care.[20] Hygienic environmental condition can not be disregarded altogether as not having some influence in predisposing the delicately growing infant to the disease.

(a) Overcrowding of the population in large cities may be contributory to the development of an unhealthy surrounding which may indirectly weaken the vitality of the children.

(b). The "theory of domestication" has been applied to explain the development of rickets in animals put in cage, taken away from the enjoyment of their natural home. It is not impossible that it may likewise be applied to human beings considering the vulnerability of the negroes to this disease in civilized countries when they seem to be exempt from it in their wild African homes. By confinement, the children are prevented or limited in their freedom to obtain the beneficial effects of physical exercise,

pure air, bright sunshine, which are obviously concerned either directly or indirectly with the proper metabolism and nutrition especially of a growing infant. The influence of sunlight in the development of the rickety state has been beautifully described by **Palm**, and is, in my opinion, worth considering. However, in addition to the above ~~contributory~~ factors, personal cleanliness ~~and~~ and domestic sanitation in general should not be neglected as contributory to the conditions that tend to increase the liability of children to the disease.[21]

21. There are no evidences at hand to show that the disease is caused by an infection.

(a) Although marasmus may not lead to the development of rickets, still it is possible that acute infectious diseases may predispose the onset of the lesions or aggravate ~~thedisease~~ them indirectly by weakening the constitutional vitality of the individual.

(b) There are sufficient evidences to show that syphilis and rickets are two different diseases. However, it is not uncommon to find the two conditions existing in the same individual. It has been stated, that syphilis predisposes the development of rickets, but it is still an unsettled question whether or not the craniotabes in syphilis is the same as that in rickets. Likewise, whether or not the enlarged spleen in syphilis presents identical histo-pathological picture as that in some cases of

rickets, is controversial.

22. Rickety lesions are presumed to be initiated by the ingestion of "rachitic food" in the same category as scurvy by the consumption of "scorbutic food". The rachitic food is assumed to be one in which the anti-rachitic factor is absent, abstracted, or considerably diminished.

23. Normal breast milk has been found superior in quality to cow's milk or any other proprietory infant food ; and, early weaning may prove to be prejudicial to the proper metabolism and nutrition of the child.

24. Too early a consumption of starchy food may upset the gastro-intestinal function of the baby, but such a disorder does not necessarily lead to the development of rickets. Sufficient reasons have been given to minimize the strength of the "lactic acid theory," although the "auto-intoxication theory" can not be held improbable until further investigation decides the contrary.

25. The insufficient amount of calcium in the food is not a factor in the production of the disease, since rickets may develop even if the supply were abundant. Other reasons have been given above to invalidate this theory of calcium dietary deficiency.

26. It may be possible, as Cheadle[7] pointed out, that the lack of fat in the diet leads to the production of some abnormal metabolic

products which may irritate the osteogenic cells and neighboring blood vessels to proliferate . This tissue overgrowth is apparently lacking the necessary factor that completes the building of permanent structure.

27. Although, as has been pointed out, the disease is characterized by deficient ossification, still it is a question whether there is decalcification of the fully-formed bone, or whether there is a lack of absorption of the calcium salts from the intestine into the blood, or whether the calcium salts brought to the osteo-plastic cells are properly utilized to form normal bones. More research works, therefore, on the metabolism of calcium are urged to clear this important point.

28. The animal experimentations conducted by our modern investigators, have advanced our views as to the specificity of the causative agent. It has been suggested by Mellanby that among the vitamines which are growth-promoting substances, the fat-soluble A may be identical with the anti-rachitic factor. On the other hand, McCollum, Shipley, Park and their co-workers, prove experimentally that the fat-soluble A has no relation with the development of the disease, but that another unidentified food accessory factor (the unknown X) in the cod liver oil,butter-fat, egg-yolk, degerminated seeds, leaves of plants, animal fat (but not in vegetable oil), is the anti-rachitic factor.

29. As a whole, the problem of the etiology and pathology of rickets is yet unsolved/Aside from a thorough study on calcium metabolism as has been above indicated, more careful and extensive works on the physiology and pathology of the organs of internal secretion and on the chemistry and pathology of the soft tissues (such as muscles, visceral organs, etc.), are indispensable to explain the pathogenesis of the disorder.

30. The role of the unknown X is still a matter of conjecture. In this connection, I may add that, while it may be assumed that it is nutritive to the growing cells, the possibility of its being a preventive or a neutralizing agent to some subsequent abnormal metabolic products in the blood detrimental to the cells, cannot be entirely ruled out. On the other hand, it may be concerned with the activity of the osteoplastic tissue (be it in the periosteum or in the "growing zone") in fixing or in utilizing th calcium salts brought to them to form a permanent normal bone structure. In other words, if the factor is deficient or absent, there may not only be a state of an abnormal stimulation of the growing cells, but also a weakened condition of the osteoblasts to absorb and deposit calcium in the growing portions of the bone. Whether this hypothetical explanation applies to the changes in the soft tissues involved in the disease, remains to be worked out. If it may be applied to the latter structure, then it is obvious that the protracted consumption of a diet destitute or deficient of unknown X, may eventually lead to the onset of rachitic lesions

in the body of an infant after he has been previously rendered vulnerable or predisposed by other factors or conditions as above enumerated.

As a closing remark, I may also add that laboratory findings would be of more value if the results are to be correlated with and corroborated by clinical observations, or vice versa. Aside from the problems I indicated above, under the Present Status, and in the"Addenda "the subject Rickets, outside of its etiological and pathological aspects, presents, from a practical public health standpoint, other side-queries worthy of serious consideration. I am referring to that phase of the relation of the disease to the health of the general population, as pointed out by the Special Report of the Medical Research Committee.[37] The Report, in speaking of the after effects of rickets, outside of the defective dentition, goes on saying:

> "Nor is this the most serious part of the evil, for the reduced resistance to other diseases of the rachitic child and animal is so marked that the causative factor of rickets may be the secret of immunity and non-immunity to many of the diseases which result in the high infantile death rate associated with urban conditions. It is a striking fact to remember that in the West of Ireland, where the infantile death rate is only 30 per 1000, rickets is very rare, whereas in poor urban districts of this country, (England) where rickets is rife, the infantile death rate ~~there~~ is from 100 to 300 per 1000. It is at least suggested that there may be some relation between rickets and the enormous death rate of infants in towns even though the disease in itself does not kill."

Of course, the above statistical figures do not warrant definite conclusions. But this apparent relationship of rickets to infant mortality and possibly to their reaction towards other infectious diseases, be it positive or otherwise, should be investigated with more care and correlated with experimental findings; and, by some such subsequent studies, with reliable data, the writer feels confident that rickets as well as other allied nutritional deficiency diseases, as beri-beri-, scurvy, etc., will be expected in the future to deserve more important merits in public health administration than they, at present, have.

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Finis. .

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